EPA/310-R-97-005

EPA Office of Compliance Sector Notebook Project:

Profile of the Pharmaceutical Manufacturing Industry

September 1997

Office of Compliance
Office of Enforcement and Compliance Assurance
U.S. Environmental Protection Agency
401 M St., SW (MC 2221-A)
Washington, DC 20460

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Electronic versions of all Sector Notebooks are available via Internet on the Enviroene World Wide Web. Downloading procedures are described in Appendix A of this document.

Cover photographs courtesy of Pharmaceutical Research and Manufacturers of America.

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Table of Contents

List of Tables

List of Figures

List of Acronyms

AFS - AIRS Facility Subsystem (CAA database)
AIRS - Aerometric Information Retrieval System (CAA database)
BIFs - Boilers and Industrial Furnaces (RCRA)
BOD - Biochemical Oxygen Demand
CAA - Clean Air Act
CAAA - Clean Air Act Amendments of 1990
CDER - Center for Drug Evaluation and Research
CERCLA - Comprehensive Environmental Response, Compensation and Liability Act
CERCLIS - CERCLA Information System
CFCs - Chlorofluorocarbons
CO - Carbon Monoxide
COD - Chemical Oxygen Demand
CSI - Common Sense Initiative
CTM - Clinical Trial Material
CWA - Clean Water Act
D&B - Dun and Bradstreet Marketing Index
ELP - Environmental Leadership Program
EPA - United States Environmental Protection Agency
EPCRA - Emergency Planning and Community Right-to-Know Act
FDA - Food and Drug Administration
FIFRA - Federal Insecticide, Fungicide, and Rodenticide Act
FINDS - Facility Indexing System
HAPs - Hazardous Air Pollutants (CAA)
HSDB - Hazardous Substances Data Bank
IDEA - Integrated Data for Enforcement Analysis
IND - Investigational New Drug
LDR - Land Disposal Restrictions (RCRA)
LEPCs - Local Emergency Planning Committees
MACT - Maximum Achievable Control Technology (CAA)
MCLGs - Maximum Contaminant Level Goals
MCLs - Maximum Contaminant Levels
MEK - Methyl Ethyl Ketone
MSDSs - Material Safety Data Sheets
NAAQS - National Ambient Air Quality Standards (CAA)
NAFTA - North American Free Trade Agreement
NAICS - North American Industrial Classification System
NCDB - National Compliance Database (for TSCA, FIFRA, EPCRA)
NCP - National Oil and Hazardous Substances Pollution Contingency Plan
NDA - New Drug Application
NEIC - National Enforcement Investigation Center
NESHAP - National Emission Standards for Hazardous Air Pollutants
NO_2 - Nitrogen Dioxide
NOV - Notice of Violation
NO_x - Nitrogen Oxides

NPDES - National Pollution Discharge Elimination System (CWA)
NPL - National Priorities List
NRC - National Response Center
NSPS - New Source Performance Standards (CAA)
OAR - Office of Air and Radiation
OECA - Office of Enforcement and Compliance Assurance
OPA - Oil Pollution Act
OPPTS - Office of Prevention, Pesticides, and Toxic Substances
OSHA - Occupational Safety and Health Administration
OSW - Office of Solid Waste
OSWER - Office of Solid Waste and Emergency Response
OW - Office of Water
P2 - Pollution Prevention
PCS - Permit Compliance System (CWA Database)
PhRMA - Pharmaceutical Research and Manufacturers of America
POTW - Publicly Owned Treatments Works
RCRA - Resource Conservation and Recovery Act
RCRIS - RCRA Information System
SARA - Superfund Amendments and Reauthorization Act
SDWA - Safe Drinking Water Act
SEPs - Supplementary Environmental Projects
SERCs - State Emergency Response Commissions
SIC - Standard Industrial Classification
SO_2 - Sulfur Dioxide
SO_x - Sulfur Oxides
TOC - Total Organic Carbon
TRI - Toxic Release Inventory
TRIS - Toxic Release Inventory System
TCRIS - Toxic Chemical Release Inventory System
TSCA - Toxic Substances Control Act
TSS - Total Suspended Solids
UIC - Underground Injection Control (SDWA)
UST - Underground Storage Tanks (RCRA)
VOCs - Volatile Organic Compounds

I. INTRODUCTION TO THE SECTOR NOTEBOOK PROJECT

I.A. Summary of the Sector Notebook Project

Integrated environmental policies based upon comprehensive analysis of air, water and land pollution are a logical supplement to traditional single-media approaches to environmental protection. Environmental regulatory agencies are beginning to embrace comprehensive, multi-statute solutions to facility permitting, enforcement and compliance assurance, education/ outreach, research, and regulatory development issues. The central concepts driving the new policy direction are that pollutant releases to each environmental medium (air, water and land) affect each other, and that environmental strategies must actively identify and address these inter-relationships by designing policies for the "whole" facility. One way to achieve a whole facility focus is to design environmental policies for similar industrial facilities. By doing so, environmental concerns that are common to the manufacturing of similar products can be addressed in a comprehensive manner. Recognition of the need to develop the industrial "sector based" approach within the EPA Office of Compliance led to the creation of this document.

The Sector Notebook Project was originally initiated by the Office of Compliance within the Office of Enforcement and Compliance Assurance (OECA) to provide its staff and managers with summary information for eighteen specific industrial sectors. As other EPA offices, states, the regulated community, environmental groups, and the public became interested in this project, the scope of the original project was expanded to its current form. The ability to design comprehensive, common sense environmental protection measures for specific industries is dependent on knowledge of several inter-related topics. For the purposes of this project, the key elements chosen for inclusion are: general industry information (economic and geographic); a description of industrial processes; pollution outputs; pollution prevention opportunities; Federal statutory and regulatory framework; compliance history; and a description of partnerships that have been formed between regulatory agencies, the regulated community and the public.

For any given industry, each topic listed above could alone be the subject of a lengthy volume. However, in order to produce a manageable document, this project focuses on providing summary information for each topic. This format provides the reader with a synopsis of each issue, and references if more in-depth information is available. The contents of each profile were researched from a variety of sources, and were usually condensed from more detailed sources. This approach allowed for a wide coverage of activities that can be further explored based upon the citations and references listed at the end of this profile. As a check on the information included, each notebook went through an external review process. The Office of Compliance

appreciates the efforts of all those who participated in this process who enabled us to develop more complete, accurate and up-to-date summaries. Many of those who reviewed this notebook are listed as contacts in Section X and may be sources of additional information. The individuals and groups on this list do not necessarily concur with all statements within this notebook.

I.B. Additional Information

Providing Comments

OECA's Office of Compliance plans to periodically review and update the notebooks and will make these updates available both in hard copy and electronically. If you have any comments on the existing notebook, or if you would like to provide additional information, please send a hard copy and computer disk to the EPA Office of Compliance, Sector Notebook Project, 401 M St., SW (2223-A), Washington, DC 20460. Comments can also be uploaded to the Enviroene World Wide Web for general access to all users of the system. Follow instructions in Appendix A for accessing this system. Once you have logged in, procedures for uploading text are available from the on-line Enviroene Help System.

Adapting Notebooks to Particular Needs

The scope of the industry sector described in this notebook approximates the national occurrence of facility types within the sector. In many instances, industries within specific geographic regions or states may have unique characteristics that are not fully captured in these profiles. The Office of Compliance encourages state and local environmental agencies and other groups to supplement or re-package the information included in this notebook to include more specific industrial and regulatory information that may be available. Additionally, interested states may want to supplement the "Summary of Applicable Federal Statutes and Regulations" section with state and local requirements. Compliance or technical assistance providers may also want to develop the "Pollution Prevention" section in more detail. Please contact the appropriate specialist listed on the opening page of this notebook if your office is interested in assisting us in the further development of the information or policies addressed within this volume. If you are interested in assisting in the development of new notebooks for sectors not already covered, please contact the Office of Compliance at 202-564-2395.

II. INTRODUCTION TO THE PHARMACEUTICAL INDUSTRY

This section provides background information on the size, geographic distribution, employment, production, sales, and economic condition of the pharmaceutical industry. Facilities described within this document are described in terms of their Standard Industrial Classification (SIC) codes.

II.A. Introduction, Background, and Scope of the Notebook

The Standard Industrial Classification (SIC) code established by the U.S. Office of Management and Budget (OMB) to track the flow of goods and services within the economy is 283 for the pharmaceuticals industry. The industry is further categorized by four 4-digit SIC codes consisting of:

Medicinals and Botanicals (SIC 2833)
Pharmaceutical Preparations (SIC 2834)
In Vivo and in Vitro Diagnostic Substances (SIC 2835)
Biological Products, except diagnostics (SIC 2836)

OMB is in the process of changing the SIC code system to a system based on similar production processes called the North American Industrial Classification System (NAICS). In the NAIC system, medicinals and botanicals are classified as NAIC 325411 and pharmaceutical preparations are classified as NAIC 325412.

According to the *U.S. Census of Manufacturers*, in 1992 the Medicinals and Botanicals and Pharmaceutical Preparations categories accounted for 64 percent of establishments and 81 percent of the value of shipments in the industry. In comparison, the In Vitro and In Vivo Diagnostic Products and Biological Products categories are relatively small. Together they accounted for the remaining 36 percent of establishments and 19% of the value of shipments in the industry. In general, the industrial processes and subsequent environmental impacts of the In Vitro and In Vivo Diagnostic Products and Biological Products categories are different from those of the Medicinals and Botanicals and Pharmaceutical Preparations categories. This notebook concentrates on the two larger categories (SIC 2833 and 2834) within SIC 283.

II.B. Characterization of the Pharmaceutical Industry

As defined by its SIC Code, the pharmaceuticals industry (SIC 283) consists of establishments that are primarily involved in fabricating or processing medicinal chemicals and pharmaceutical products. The industry also includes establishments that formulate pharmaceutical products and are involved in grinding, grading, and milling of botanical products. The Census of Manufacturers defines an establishment as a single physical location or a

facility where manufacturing occurs. If more than one distinct line of manufacturing occurs at the same location, the Bureau of Census requires separate reports for each activity.

Although the industry is part of the two-digit SIC code 28 for Chemicals and Allied Products, it differs significantly from the rest of the chemicals industry in its industrial processes and regulatory requirements. For example, in its industrial processes, the pharmaceuticals industry uses more batch operations than the chemicals industry as a whole. Since some of the bulk manufacturing operations involve extracting relatively small, highly concentrated quantities of active ingredients from much larger volumes of raw material, the industry's production yield for these operations is correspondingly low.

The pharmaceuticals industry also receives extensive regulatory oversight by the U.S. Food and Drug Administration (FDA). In 1996, the Center for Drug Evaluation and Research, FDA approved 131 new drug applications (NDAs), of which 53 were new molecular entities. According to the Congressional Office of Technology Assessment (OTA) in 1993, it costs an average of $359 million to develop a new drug and complete the drug approval process. Total drug development and agency review time averaged 15.3 years for drugs approved from 1990 through 1995. More information on the typical industrial processes and regulatory requirements of this industry is provided in Sections III and VI, respectively.

When a pharmaceutical company discovers a compound that may have medical potential, the company usually applies for a patent. Patents are valid for 20 years from the date of application. Any drug made from the compound may be marketed only after approval by the federal Food and Drug Administration (FDA). The drug development process, beginning with initial toxicology testing, followed by clinical trials for safety and effectiveness, and review of the application by the FDA averages fifteen years. When the company's patent or period of exclusivity has expired, other companies may rely on the original manufacturer's data on safety and effectiveness to obtain approval to market a generic version of the drug. Companies wanting to manufacture the same drug once it is off-patent are required to obtain FDA marketing approval, based on evidence that the generic version is "bioequivalent," i.e., differs in the rate and extent of drug absorption by no more than 25 percent nor less than the 20 percent from the original drug (FDA, 1996). While companies that specialize in the development and marketing of brand-name, innovator drugs[1] may have subsidiaries that

[1] The term "brand name" is used interchangeably with "pioneer drug" or "innovator's drug product". The terms reflect the fact that the drug product is the first to contain a particular active ingredient or ingredients to receive FDA approval for a specified use. The term "generic" drug is used to describe a product that contains the same active

manufacture generic products, most generic drug companies do not conduct research intended to identify and develop innovator drugs (PhRMA, 1997).

Because of the high cost and time to approval, effective patent protection is an essential component in the decision to invest in drug development and marketing. This is especially true for international companies interested in marketing drugs in several countries, each with its own approval procedure and marketing requirements. While the International Conference on Harmonization is proposing harmonized rules for drug registration and approval for Europe, Japan and the United States, each country retains its own approval system. In other countries, especially developing countries, the issue of adequate patent protection is a central concern of pharmaceutical manufacturers (PhRMA, 1997).

Discovery of new compounds followed by further research and development (R&D) is one of the primary functions of the industry. The pharmaceutical production process starts with an extensive research stage, which can last several years. Following the discovery of a new drug that appears to have efficacy in treating or preventing illness, pre-clinical tests and clinical trials are conducted. Then a New Drug Application (NDA) is submitted to the FDA for approval. According to a primary trade association for pharmaceutical companies producing brand name drugs, the Pharmaceutical Research and Manufacturers of America (PhRMA), it takes an average of 15 years to bring a new drug to market, from time of discovery to approval (PhRMA, 1996). It is only after FDA approval has been secured that market distribution in the U.S. can begin.

The competition for discovering new drugs and bringing them to market is extremely high. As a result, a significant proportion of the industry's sales are reinvested into research and development (R&D). According to PhRMA, total R&D expenditures, both domestically and abroad, by its members, will be close to $19 billion dollars in 1997. PhRMA estimates that over 21% of total sales will be reinvested into R&D by its members (PhRMA, 1997).

II.B.1. Product Characterization

The pharmaceutical industry manufactures bulk substance pharmaceutical intermediates and active ingredients which are further processed into finished products.

Medicinals and Botanicals (SIC 2833)

Companies in the Medicinals and Botanicals industry category are primarily

ingredients but not necessarily the same excipients (inactive ingredients) as a so-called "pioneer drug".

engaged in 1) manufacturing bulk organic and inorganic medicinal chemicals and their derivatives and 2) processing (grading, grinding, and milling) bulk botanical drugs and herbs. The industry is made up of establishments or facilities that manufacture products of natural origin, hormonal products, and basic vitamins, as well as those that isolate active medicinal principals such as alkaloids from botanical drugs and herbs (OMB, 1987). These substances are used as active ingredients for the Pharmaceutical Preparations industry category. Companies often produce both Medicinals and Botanicals and Pharmaceutical Preparations at the same facility.

Pharmaceutical Preparations (SIC 2834)

The Pharmaceutical Preparations industry category is made up of companies that manufacture, fabricate, and process raw materials into pharmaceutical preparations for human and veterinary uses. Finished products are sold in various dosage forms including, for example, tablets, capsules, ointments, solutions, suspensions, and powders. These are 1) preparations aimed for use mainly by dental, medical, or veterinary professionals, and 2) those aimed for use by patients and the general public (OMB, 1987). A more in depth discussion of these finished products is provided in Section III.A.3. Pharmaceutical products also are often classified in terms of their availability to the general public.

Both prescription and over-the-counter (OTC) drugs are available to the public. Prescription drugs can be purchased only with a prescription from a licensed health care professional authorized to prescribe, while OTC drugs may be purchased without a prescription. The FDA will consider approving the switch of a drug from prescription to OTC when the manufacturer presents evidence that consumers can self-diagnose the condition for which the drug is approved, i.e., cold or seasonal allergy, and directions for use can be written for the consumer (PhRMA, 1997).

In Vivo and In Vitro Diagnostic Substances (SIC 2835) and Biological Products (SIC 2836)

The In Vivo and In Vitro Diagnostic Substances industry category (SIC 2835) includes facilities that manufacture in vivo (tested inside a living organism) and in vitro (tested outside of a living organism) diagnostic substances. They produce chemical, biological, and radioactive substances used in diagnosing and monitoring health. The Biological Products industry category (SIC 2836) produces bacterial and virus vaccines, toxoids, serums, plasmas, and other blood derivatives for human and veterinary use, other than in vitro and in vivo diagnostic substances (OMB, 1987).

II.B.2. Industry Size

According to the *U.S. Census of Manufacture*s for the pharmaceuticals

industry as a whole (SIC 283), in 1992 there were a total of 1,425 establishments employing 194,000 people (excluding Puerto Rico). It is possible that some of the smaller facilities identified by the Census are actually sales, marketing or distribution centers in which no manufacturing operations take place. Such possible misclassifications have no significant effect on the census statistics other than on the number of companies and establishments. (U.S. Department of Commerce, 1995) The value of total shipments was over $67 billion (see Table 1). Pharmaceutical Preparations (SIC 2834) was the largest sector in terms of number of facilities (48 percent), employment (63 percent), and value of shipments (75 percent). The remaining facilities, employment, and value of shipments were divided evenly among the remaining sectors within the industry. One exception is the In Vivo and In Vitro Diagnostic Products sector (SIC 2835) which claims a higher portion of employment than SIC codes 2833 and 2836. Figure 1 displays the value of shipments by sector, and Figure 2 displays employment by sector.

A relatively significant number of pharmaceutical establishments are located in Puerto Rico. This is in part the result of the federal government's policy decision to encourage job creation by offering tax incentives to manufacturers to locate new plants in Puerto Rico. A 1996 tax law phases-out those tax incentives over the next ten years.

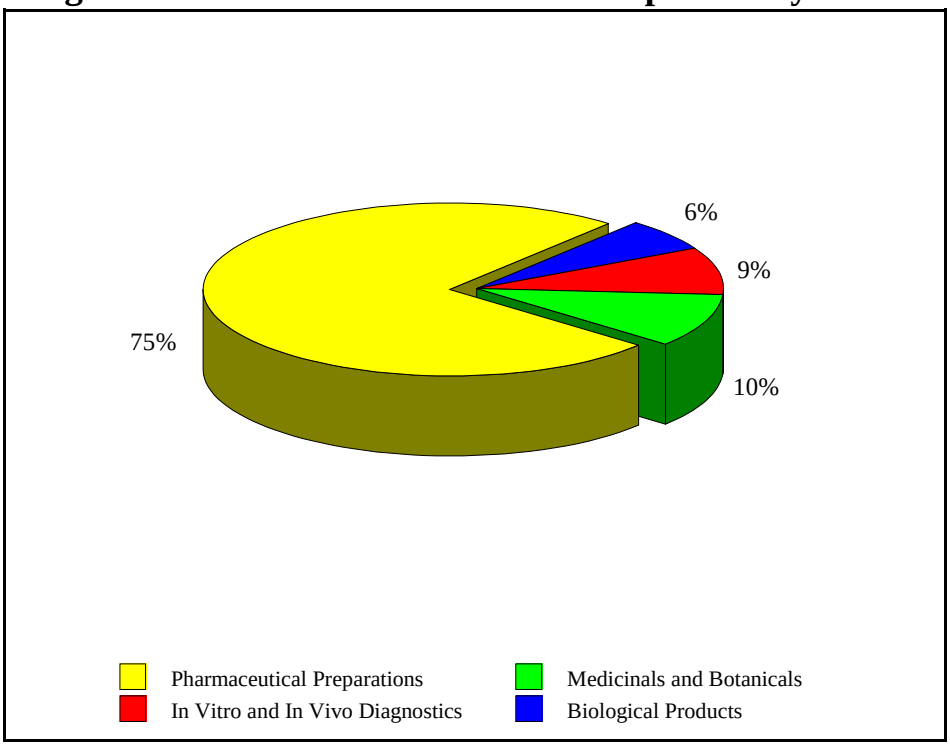
The effects of the tax incentive are illustrated by the concentration of pharmaceutical plants in Puerto Rico. According to the 1992 Economic Census of Outlying Areas, which covers statistics for Puerto Rico, there were a total of 88 establishments in Puerto Rico. Of these 88, 74 establishments were in the Pharmaceutical Preparations industry, 8 were in the Medicinals and Botanicals industry, and the remaining six establishments were in the In Vitro and In Vivo Diagnostic Products industry, and the Biological Products, except diagnostic substances industry. The total value of shipments of the 88 establishments located in Puerto Rico was about $12 billion. Pharmaceutical Preparations accounted for about 92 percent of this. The pharmaceutical industry in Puerto Rico employed about 25,000 people in the 88 establishments in 1992.

Table 1: Summary Statistics for the Pharmaceutical Industry							
	50 STATES				PUERTO RICO		
Industry	Number of Establishments	Number of Companies[1]	Value of Shipments (millions of dollars)[2]	Employment (000's)	Number of Establishments	Value of Shipments (millions of dollars)[2]	Employment (000's)
SIC 2833	225	208	6,438	13	8	N/A[3]	N/A[3]
SIC 2834	691	585	50,418	123	74	11,097	22
SIC 2835	234	205	6,838	40	5	477	1
SIC 2836	275	193	3,974	18	1	N/A[3]	N/A[3]
Total	1,425	1,191	67,668	194	88	11,924	25

Source: *1992 Census of Manufacturers, Industry Series: Drugs, US Department of Commerce, Bureau of the Census, 1995 and 1992 Economic Census of Outlying Areas, Manufacturers: Puerto Rico, US Department of Commerce, Bureau of the Census, 1994.*

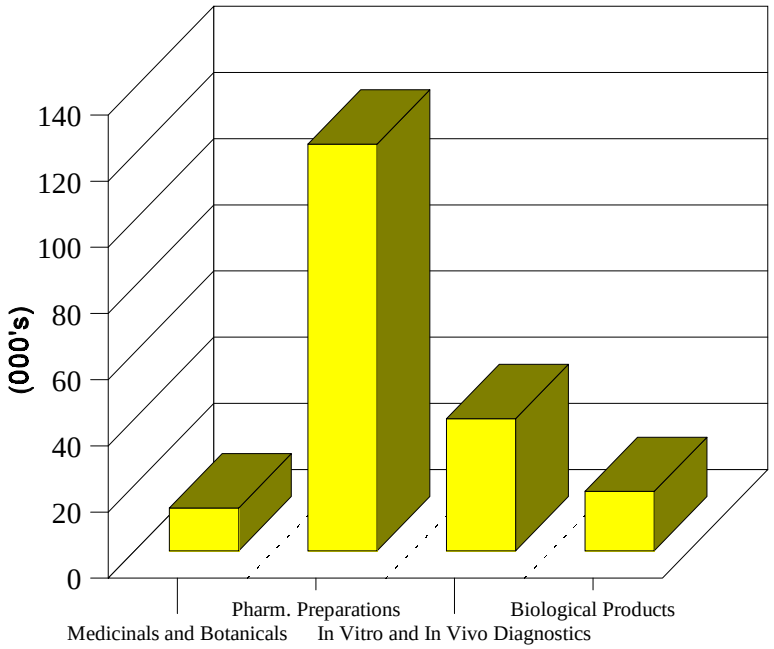
[1]Defined as a business organization consisting of one establishment or more under common ownership or control.
[2]Value of all products and services sold by establishments in the pharmaceuticals industry.
[3]Certain census data are not available for Puerto Rico. Information is withheld to avoid disclosing data for individual facilities.

Figure 1: Percent of Total Value of Shipments by Sector



Source: 1992 U.S. Census of Manufacturers.

Figure 2: Employment in the Pharmaceutical Industry



Source: 1992 U.S. Census of Manufacturers.

As shown in Table 2, many facilities within the pharmaceutical industry are small. Almost 70 percent of the facilities employ fewer than 50 people. However, a relatively small number of large companies account for a large portion of the total value of shipments, as well as employment. For example, according to the 1992 U.S. Census of Manufacturers, only 36 facilities (less than three percent) employed more than 1,000 people in the 50 states (i.e., not including Puerto Rico). However, these 36 facilities accounted for over 38% of the total value of shipments for the industry. In comparison, 968 facilities (almost 70 percent) employ fewer than 50 people. However, these facilities accounted for less than four percent of the industry's value of shipments.

Table 2: Pharmaceutical Industry (SIC 283) Facility Size[1]			
Number of Employees	**Number of Facilities**	**Percent of Total Facilities (%)**	**Percent of Total Value of Shipments (%)**
fewer than 10	479	34	0.6
10 to 49	489	34	3.2
50 to 249	292	20	19
250 to 999	129	9.1	39[2]
1,000 or more	36	2.5	38[2]
Total	1,425	100	100

Source: *1992 Census of Manufacturers, Industry Series: Drugs, Bureau of the Census, 1995.*

[1] Does not include Puerto Rico - information withheld to avoid disclosing data for individual facilities.

[2] Some information withheld to avoid disclosing individual facility data. Values may be somewhat higher.

Medicinals and Botanicals (SIC 2833) and Pharmaceutical Preparations (SIC 2834)

The establishment size distributions for Pharmaceutical Preparations and Medicinals and Botanicals are similar (see Table 3). The Pharmaceutical Preparations sector, however, has a somewhat higher proportion of large facilities. As is the case with the pharmaceuticals industry as a whole, a relatively small number of large establishments account for the majority of the total value of shipments for the Pharmaceutical Preparations industry. Value of shipment data is not available by establishment size for the Medicinals and Botanicals sector.

Table 3: Employment Size Distribution for Medicinals and Botanicals and Pharmaceutical Preparations Establishments [1]						
	Medicinals and Botanicals			**Pharmaceutical Preparations**		
Number of Employees	**Number of Facilities**	**Percent of Facilities**	**Percent of Value of Shipments**	**Number of Facilities**	**Percent of Facilities**	**Percent of Value of Shipments**
< than 10	104	46	N/A[2]	225	33	0.4
10 to 49	76	34	N/A[2]	211	30	2
50 to 249	35	16	N/A[2]	142	21	10
250 or more	10	4	N/A[2]	113	16	88
Total	225	100	100	691	100	100

Source: *1992 U.S. Census of Manufacturers.*

[1] Not including Puerto Rico.

[2] Information has been withheld to avoid disclosing individual establishment data.

Table 4 lists the largest U.S. pharmaceutical companies in terms of U.S. prescription sales.

Table 4: Top U.S. Pharmaceutical Companies by Sales

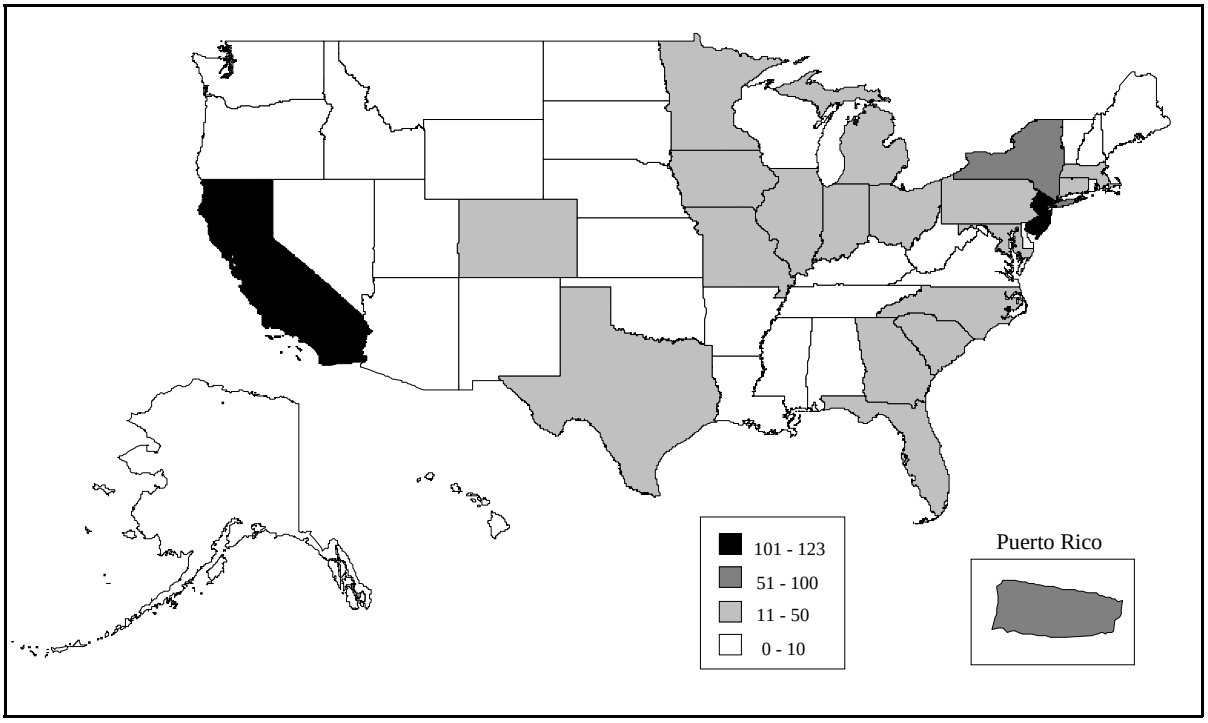
Rank	Company	1996 Rx Sales (millions of dollars)
1	Glaxo Wellcome	5,803
2	Johnson & Johnson	5,275
3	American Home Products	5,251
4	Bristol-Myers Squibb	5,160
5	Merck & Co	5,026
6	Pfizer	4,511
7	Novartis	3,786
8	SmithKline Beecham	3,589
9	Lilly	3,567
10	Abbott	3,423
11	Schering-Plough	3,272
12	Hoechst Marion Roussel	2,474
13	Roche	2,316
14	Amgen	1,860
15	Bayer	1,854

Source: *IMS America.*

II.B.3. Geographic Distribution

The U.S. pharmaceuticals industry has traditionally been concentrated in New Jersey, California, and New York (see Figure 3). These three states account for about one third of the facilities, employees, and value of shipments. Historically, the industry concentrated here because these were vocational centers. Other states, such as Massachusetts, North Carolina and Maryland, have seen recent growth in the pharmaceuticals industry, especially in biotechnology and research and development.

Figure 3: Geographic Distribution of Pharmaceutical Facilities (SIC 2833 and 2834)



Source: 1992 U.S. Census of Manufacturers.

A significant number of pharmaceutical establishments are also located in Puerto Rico. According to the *1992 Economic Census of Outlying Areas*, which covers statistics for Puerto Rico, there were a total of 88 pharmaceuticals establishments in Puerto Rico accounting for almost $12 billion in shipments. Eighty two of these establishments were in the Pharmaceutical Preparations and Medicinals and Botanicals sectors. These establishments accounted for 11 percent of all employment and 15 percent of the value of shipments for these sectors. The driving force behind the pharmaceuticals industry concentrating in Puerto Rico over the years are tax incentives specifically directed at the industry.

Many U.S. firms have facilities abroad or own foreign companies in which both R&D and production of pharmaceuticals are conducted. According to PhRMA, in 1996 its member firms employed close to 165,000 people overseas in the production of prescription pharmaceuticals. Of these, about 42% were employed in Western Europe. The next largest region for overseas employment by PhRMA member companies is Latin America and the Caribbean, with 20 percent (PhRMA, 1996). Recently, a number of pharmaceutical companies are moving production to Ireland. Similarly, many foreign owned pharmaceutical firms operate pharmaceutical research and development and production facilities in the U.S.

II.B.4. Economic Trends and International Competition

Changes in the U.S. Health Care Industry

During the early 1990s the United States pharmaceutical industry faced major challenges associated with the changing nature of health care delivery coupled with intense market competition. In 1995 about 62 percent of prescriptions were paid for by insuring third parties, up from 39 percent in 1990. Third parties, including managed care organizations and Medicaid, consider cost in choosing which drugs are approved for reimbursement. Techniques such as substituting generic drugs for branded drugs are also used. Low priced generic drugs rapidly capture a large share of prescriptions once the originating drug's patent expires. Likewise, intense R&D rivalries between companies now mean that new products may have major competition within months after their FDA approval, as was the case for three competing protease inhibitors approved between December 1995 and April 1996. Companies have responded to shorter product life cycles and cost containment pressures by forming an increasing number of strategic alliances and merging. However, a steady stream of new product introductions has contributed to steady industry growth driven by an increasing volume of prescriptions. In 1997, research-based companies' net sales in the United States are projected to reach $66.1 billion, a 5.5 percent increase over 1996 (PhRMA, 1997).

Consolidation of the Pharmaceuticals Industry

Competitive pressures are forcing many companies to restructure and form mergers and strategic alliances. Increasing competition from both domestic and foreign firms, as well as from the generic drug market, has forced mergers between the larger pharmaceutical companies and mid-sized companies. In 1989, three major mergers occurred between large and mid-sized pharmaceutical companies. In 1995, this number increased to seven. In 1996, there were three mergers.

As a result of generic competition, some brand name firms are becoming involved with companies that manufacture generic drugs by purchasing existing companies, setting up their own generic drug ventures, or forming partnerships (PhRMA, 1996). Also, many smaller biotech and R&D companies are merging with large pharmaceutical companies. Strategic alliances often involve domestic and foreign pharmaceutical companies, biotech firms, university research centers, government agencies such as the National Institute of Health, and contract research organizations. Such mergers and alliances allow companies to draw upon each others' research expertise, bring products to market more rapidly, and more effectively market products once they are approved by FDA.

Changes in Geographical Concentrations

An increasing number of establishments owned by U.S. companies are locating outside the U.S. A number of forces are driving these changes, including the growing international market for pharmaceutical products, foreign registration requirements and patent laws, laws allowing sales only if the products are manufactured in the country; and tax incentives.

International Trade and Competition

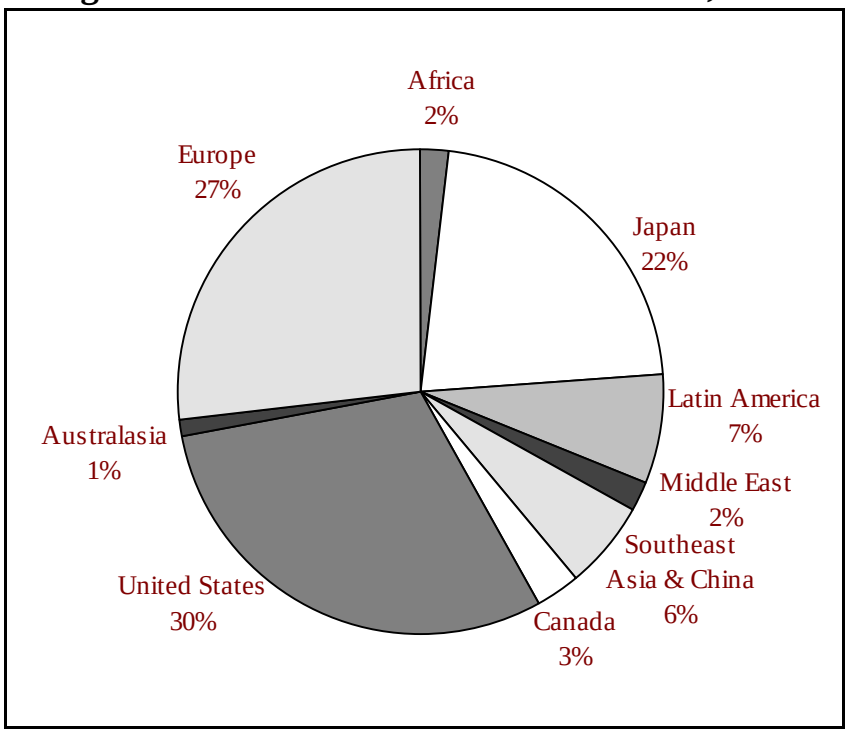
The U.S. pharmaceuticals industry accounts for about one-third of all pharmaceuticals marketed worldwide (see Figure 4). The major U.S. trading partners are Europe, Japan, Canada, and Mexico. The largest importer of U.S. pharmaceuticals is the European Community (EC). In 1993, the EC alone imported nearly 50% of all U.S. exports (ITA, 1994). Canada and Mexico combined imported 15 percent of all U.S. exports of pharmaceutical products in 1993. The North American Free Trade Agreement (NAFTA), however, has increased the volume of trade with Canada and Mexico in recent years.

Although Japan still remains one of the largest importers of U.S. pharmaceuticals, Japanese pharmaceutical companies have been investing heavily in their own R&D, thereby reducing Japan's import share of U.S. exports in recent years.

In 1993, European and Japanese pharmaceutical companies accounted for 27 percent and 22 percent of all pharmaceuticals marketed worldwide, respectively (PhRMA, 1996). China and the countries of the former Soviet Union are potentially large markets for U.S. pharmaceuticals. However, China is also increasing its production of pharmaceuticals and the former countries of the Soviet Union pose some major challenges for U.S. producers in terms of testing and licensing regulations (International Trade Administration, 1994).

Major issues affecting the international competitiveness of U.S. pharmaceutical firms include price controls and intellectual property protection abroad. Other trade barriers include foreign pricing systems that favor locally produced pharmaceuticals, discriminatory registration requirements, and requirements that foreign companies enter into joint ventures with domestic firms.

Figure 4: World Sales of Pharmaceuticals, 1995



Source: *Pharmaceutical Research and Manufacturers of America, 1997 based on data provided by IMS America, 1996.*

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III. INDUSTRIAL PROCESS DESCRIPTION

This section describes the major industrial processes within the pharmaceutical industry, including the materials and equipment used, and the processes employed. The section is designed for those interested in gaining a general understanding of the industry, and for those interested in the inter-relationship between the industrial process and the topics described in subsequent sections of this profile -- pollutant outputs, pollution prevention opportunities, and Federal regulations. This section does not attempt to replicate published engineering information that is available for this industry. Refer to Section IX for a list of reference documents that are available.

This section specifically contains a description of commonly used production processes, associated raw materials, and the materials either recycled or transferred off-site. This discussion, coupled with schematic drawings of the identified processes, provides a description of where wastes may be produced in the process. A more in-depth description of the major wastes produced by pharmaceutical manufacturing can be found in Section III.B.

Additionally, it is important to understand the regulatory framework in which pharmaceutical products are manufactured. To protect the public from unsafe or ineffective pharmaceutical products, Congress established a stringent regulatory system to control the research and development, manufacture and marketing of pharmaceutical products. The US Food and Drug Administration (FDA) was delegated the responsibility for: (i) evaluating the safety and efficacy of new drugs; (ii) determining if the benefits of the drug outweigh the risks and warrant approval for sale; and (iii) reviewing toxicological performance of active pharmaceutical ingredients. For most new pharmaceutical compounds, FDA oversight begins soon after the discovery of the compound.

III.A. Industrial Processes in the Pharmaceutical Industry

The production of pharmaceutical products can be broken down into three main stages: 1) research and development; 2) the conversion of organic and natural substances into bulk pharmaceutical substances or ingredients through fermentation, extraction, and/or chemical synthesis; and 3) the formulation of the final pharmaceutical product.

III.A.1. Research and Development

New drug development involves four principal phases: Pre-Clinical Research and Development; Clinical Research and Development; Review of New Drug Application; and Post Marketing Surveillance. Pre-Clinical Research and Development begins after a promising compound has been discovered and isolated in the laboratory. In this phase, the compound is subjected to extensive laboratory and animal tests to determine whether the compound is biologically active and safe. The average time to complete this phase is six

years.

After completing the Pre-Clinical Research and Development and before testing the drug in humans, an application is filed with FDA known as an Investigational New Drug Application (IND). The application must show the results of the pre-clinical testing and detail the plans for human clinical tests. It must also contain information about the chemical structure of the compound and a general description as to how the compound is manufactured.

Clinical Research and Development is typically conducted in three phases, with each phase involving progressively more people. The first phase, which typically lasts about a year, is aimed at establishing the drug's safety and involves a small number of healthy volunteers. The second phase, which lasts about two years, helps the scientists determine the drug's effectiveness. In the third phase, the drug is used in clinics and hospitals, and scientists must confirm the results of earlier tests and identify any adverse reactions. Altogether the three phases of Clinical Research and Development take about six years.

In the first phase of Clinical Research and Development, a small amount of the compound is manufactured in a pilot plant for use in the clinical trials. This batch of compound is called Clinical Trial Material (CTM). At this time, the manufacturing steps of the compound are also optimized and improved. During this phase, attention to waste minimization considerations is most effective.

After Clinical Research and Development is completed, the company files, with the FDA, a New Drug Application (NDA) containing comprehensive data about the compound. The NDA must include data to demonstrate that the drug is safe and effective for use under the conditions described in its labeling. FDA regulations require that the NDA contain specific and detailed information on: the components and composition of the drug; the methods and controls used in the manufacturing; processing and packaging of the drug; and, data from all pre-clinical and clinical investigations. In 1993, the median total approval time for NDAs was 21 months. This has been significantly reduced and in 1996, the median total approval time for NDAs was 15 months.

Each step in the manufacturing process, and the identity and quality of each ingredient used in the process, must be specified in the NDA and approved by the FDA. Once the NDA is approved, certain changes cannot be made without the filing and approval by the FDA of a supplemental application, known as an SNDA. The level of reporting depends on the type of change and may require substantial investment of resources to implement. FDA approval may take several years to obtain depending on the nature of the

change, and some changes even require new clinical studies.

Based on data from a 1995 study by the Center for the Study of Drug Development at Tufts University, a pharmaceutical Research and Development (R&D) facility discovering and developing a new medicinal agent will evaluate approximately 5,000 to 10,000 compounds. About 250 of these substances may hold therapeutic promise and enter preclinical testing. However, only about five will go on to limited human clinical testing. Subsequently, only one, after 15.3 years of research and development, will be introduced commercially as a new drug (PhRMA, 1997).

Basic research is responsible for identifying and isolating or synthesizing each new chemical entity that will be evaluated for its potential therapeutic effectiveness. Once a lead compound has been identified and characterized, some 1,000 related chemical substances will be synthesized and studied by laboratory assay systems. These assay systems are designed to identity which compounds exhibit the most specific and potent biological effect. For each compound tested, generally some 5-10 separate chemical reactions will be needed to synthesize the compound. The results of biological testing will then guide the direction of subsequent synthetic operations. If the results are unsatisfactory, then the process starts anew.

Should a substance show promise in the laboratory assays, limited animal studies are started. If there is no activity in the animal, other related compounds will be evaluated or the program will be discontinued. Once biologically active substances are identified, they will undergo further chemical modification to refine their efficacy and safety.

Once an active candidate has been identified, it will be proposed for formal development. Pharmaceutical development includes the evaluation of synthetic methods on a larger scale and the assessment of various ways of formulating the drug to provide optimum delivery. Up to this point, only small amounts have been synthesized for evaluation. More will be needed for the extensive animal testing required by FDA. Even larger amounts will be required for the extensive clinical studies in humans required before federal approval.

III.A.2. Production of Bulk Pharmaceutical Substances

Bulk pharmaceutical substances typically consist of structurally complex organic chemical compounds which are manufactured via a series of intermediate steps and reactions under precise conditions. These substances are used in the manufacture of the dosage form of a formulated pharmaceutical product and are manufactured by: (1) chemical synthesis; (2) fermentation; (3) isolation/recovery from natural sources, or (4) a

combination of these processes. Examples of different drugs produced by each of these processes are presented in Table 5.

Table 5: Examples of Pharmaceutical Products by Bulk Manufacturing Process

Chemical Synthesis	Natural Product Extraction	Fermentation
Antibiotics Antihistamines Cardiovascular Agents Central Nervous System (CNS) Stimulants CNS Depressants Hormones Vitamins	Antineoplastic Agents Enzymes and Digestive Aids CNS Depressants Hematological Agents Insulin Vaccines	Antibiotics Antineoplastic Agents Therapeutic Nutrients Vitamins Steroids

Most pharmaceutical substances are manufactured utilizing "batch" processes. In a batch process, a particular substance or "intermediate"[2] is manufactured in a "campaign" for periods ranging from a few days to several months until sufficient material is manufactured to satisfy the projected sales demand. At the end of the manufacturing campaign, another pharmaceutical intermediate or substance is made. The same equipment with potentially different configurations and the same operating personnel are often used to make a different intermediate or substance, utilizing different raw materials, executing different processes, and generating different waste streams.

When the same equipment is used for manufacturing different intermediates and/or different bulk substances, the equipment is thoroughly cleaned and validated prior to its reuse. Where cleaning of a specific type of equipment is difficult or where a sufficient volume of a certain intermediate or bulk substance is made every year, the equipment may be dedicated to the batch manufacturing of a particular intermediate or bulk substance. Where the equipment is dedicated to the production of successive batches of the same intermediate or bulk substance, the equipment may not be washed and cleaned between batches. Instead, the cleaning schedule will depend on whether there is a potential for carryover of contaminants or degraded materials that could affect the final product.

The specific methods and materials (e.g., water, steam, detergents, and/or organic solvents) used to clean the equipment are based on the ability of the cleaning process to remove residues of raw materials, intermediates, precursors, degradation products, and isomers (FDA, 1996).

[2] An intermediate is a material produced during a manufacturing process that must undergo further molecular change or processing before it becomes a bulk pharmaceutical substance.

Raw materials are checked for their identity and quality before use in the manufacturing processes. Additionally, in-process testing, as well as quality assurance/quality control (QA/QC) testing in onsite laboratories, is performed during drug product manufacturing. In-process testing may include simple pH measurements or checks on color, while QA/QC testing typically includes more sophisticated analyses such as chromatography. "Upon completion of the manufacturing operation, batch-production records are checked by competent and responsible personnel for actual yield against theoretical yield of a batch and to ensure that each step has been performed and signed for" (McGraw Hill Encyclopedia of Technology).

Chemical Synthesis

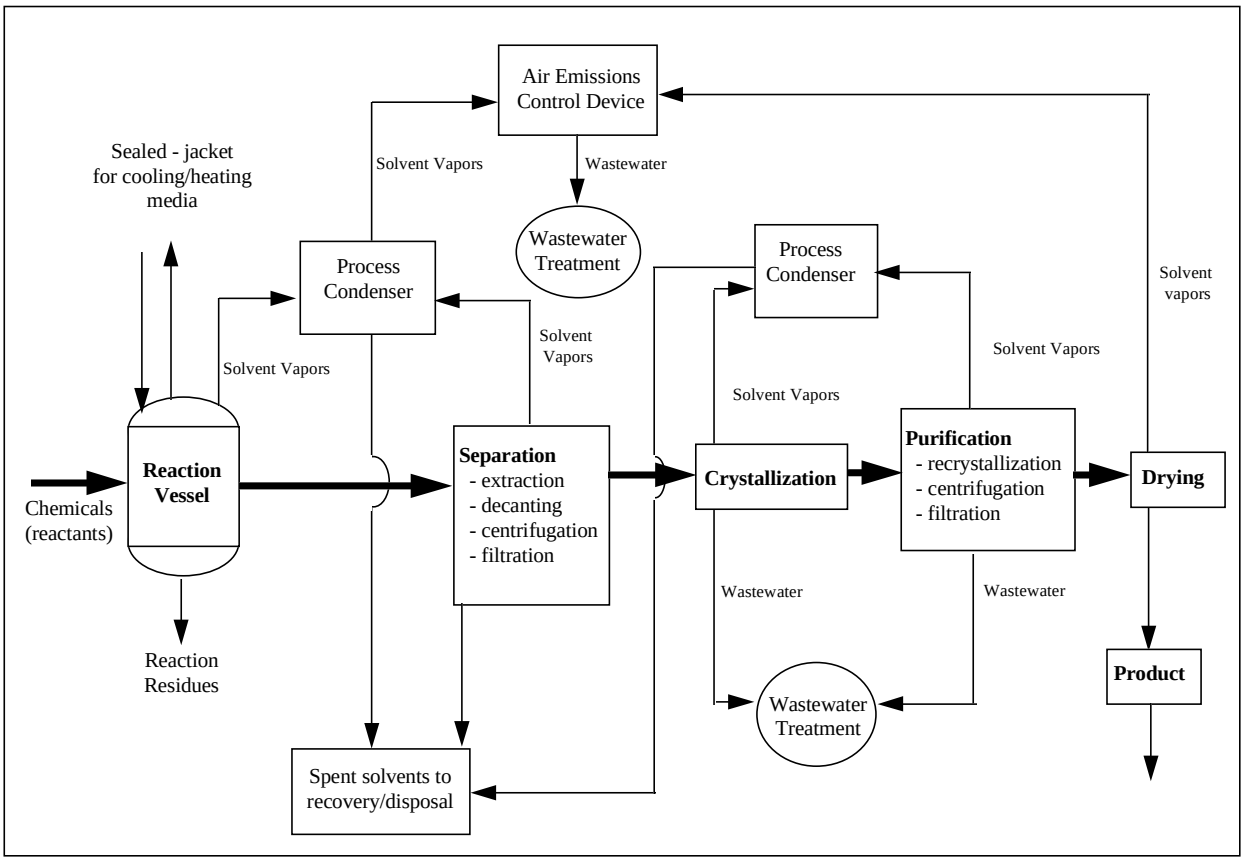
Most of the compounds used today as pharmaceutical products are prepared by chemical synthesis, generally by a batch process (Watthey, 1992). Cardiovascular agents, central nervous system agents, vitamins, antibiotics, and antihistamines are just a few examples of the bulk pharmaceutical substances made by this process.

The manufacture of pharmaceutical compounds using chemical synthesis involves a complex series of processes including many intermediate stages and chemical reactions performed in a step-by-step fashion. Depending on the process, the operator (or a programmed computer) adds reagents, increases or decreases the flow rate of chilled water or steam, and starts and stops pumps to draw the reactor contents into another vessel. At other stages in the process, solutions may be pumped through filters or centrifuges, recycled within the process, or pumped to recycling or disposal facilities. Co-products, such as salts, may be sold for reuse. Spent acids, metals, and catalysts may be recovered and reused onsite or sold for reuse.

The material from each intermediate step may be isolated and transferred to the next step of the process for continued processing until the final compound is derived. These steps may be all conducted at the same manufacturing site, or if the intermediate is isolated, it may be transferred to another site for further processing.

It is impossible to provide a single process flow diagram for this industry since each bulk pharmaceutical substance is different in its manufacture and several intermediates may be produced in a step-wise fashion prior to the manufacture of the final active ingredient. However, an example chemical synthesis process has been provided as Figure 5 to show the equipment used and where wastes or emissions might be generated.

Figure 5: Simplified Process Flow Diagram for Chemical Synthesis



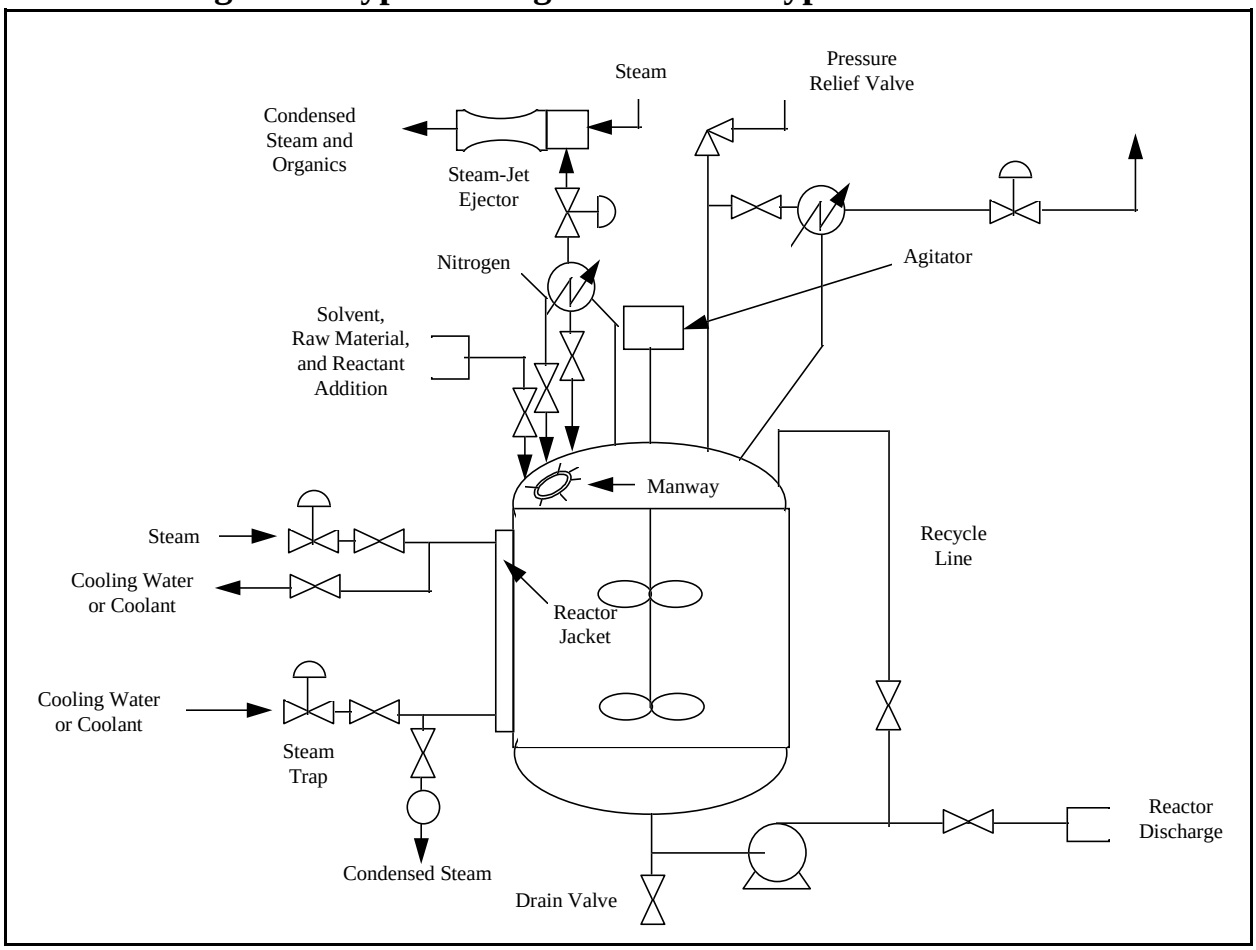
Source: Adapted from *Economic Impact and Regulatory Flexibility Analysis of Proposed Effluent Guidelines for the Pharmaceutical Manufacturing Industry, 1995.*

Reactors

The most common type of reactor vessel is the kettle-type reactor. These reactors typically range in capacity from 50 to several thousand gallons. The vessels are made of either stainless steel or glass-lined carbon steel.

A diagram of a typical reactor vessel is shown in Figure 6. "Reactors are equipped to provide a range of capabilities that may be required during the batch reaction step. This equipment may include: a jacket for heating and cooling, hookups for charging raw materials and for discharging the contents of the reactor, an agitation and recycle line for mixing, control systems for temperature and pressure, a condenser system for controlling vent losses, a return line for refluxing condensables, a steam ejector for vacuum operation, a nitrogen supply for padding and purging the reactor, and a manway for taking samples and adding solid catalysts, reactants, and other solid materials to the reactor" (USEPA 1993).

Figure 6: Typical Design of a Kettle-Type Batch Reactor



Source: Adapted from *Control of Volatile Organic Compound Emissions from Batch Processes, EPA Guideline Series, 1993.*

Raw materials or ingredients, including solvents, used to produce the intermediate or bulk substances are charged into the reactor vessel. Liquid ingredients are drawn into the reactor either by pumping or through vacuum from drums and storage tanks. Solids may be charged manually or via mechanical means such as through a vacuum system.

Once the reactor vessels are charged with the raw materials, the reaction takes place. "The reactor can be operated at atmospheric pressure, elevated pressure, or under vacuum. Because of their flexibility, reactors may be used in a variety of ways. Besides hosting chemical reactions, they can act as mixers, heaters, holding tanks, crystallizers, and evaporators." (USEPA, 1979) Typical reactions performed include alkylations, hydrogenations, brominations, etc. Temperature, pressure, and the degree of mixing are carefully monitored to achieve the desired product and to ensure worker safety.

Reactors are often attached to process condensers to recover solvents from process operations. They are also often attached to other air pollution control devices to remove volatile organics or other compounds from vented gases. Depending on the reaction being carried out, a reactor may also be attached to a distillation column for solvent separation and recovery.

Separation

Several separation mechanisms are employed by the pharmaceutical industry including extraction, decanting, centrifugation, and filtration. These mechanisms may be employed jointly or individually, in multiple stages, to separate the intermediate or bulk substance from the reaction solution and to remove impurities. Crystallization is another common technique used to separate the desired active ingredient or intermediate from the reaction mixture. Because crystallization is widely used in conjunction with other separation techniques, it is presented separately from the other separation techniques shown in Figure 5 and discussed below.

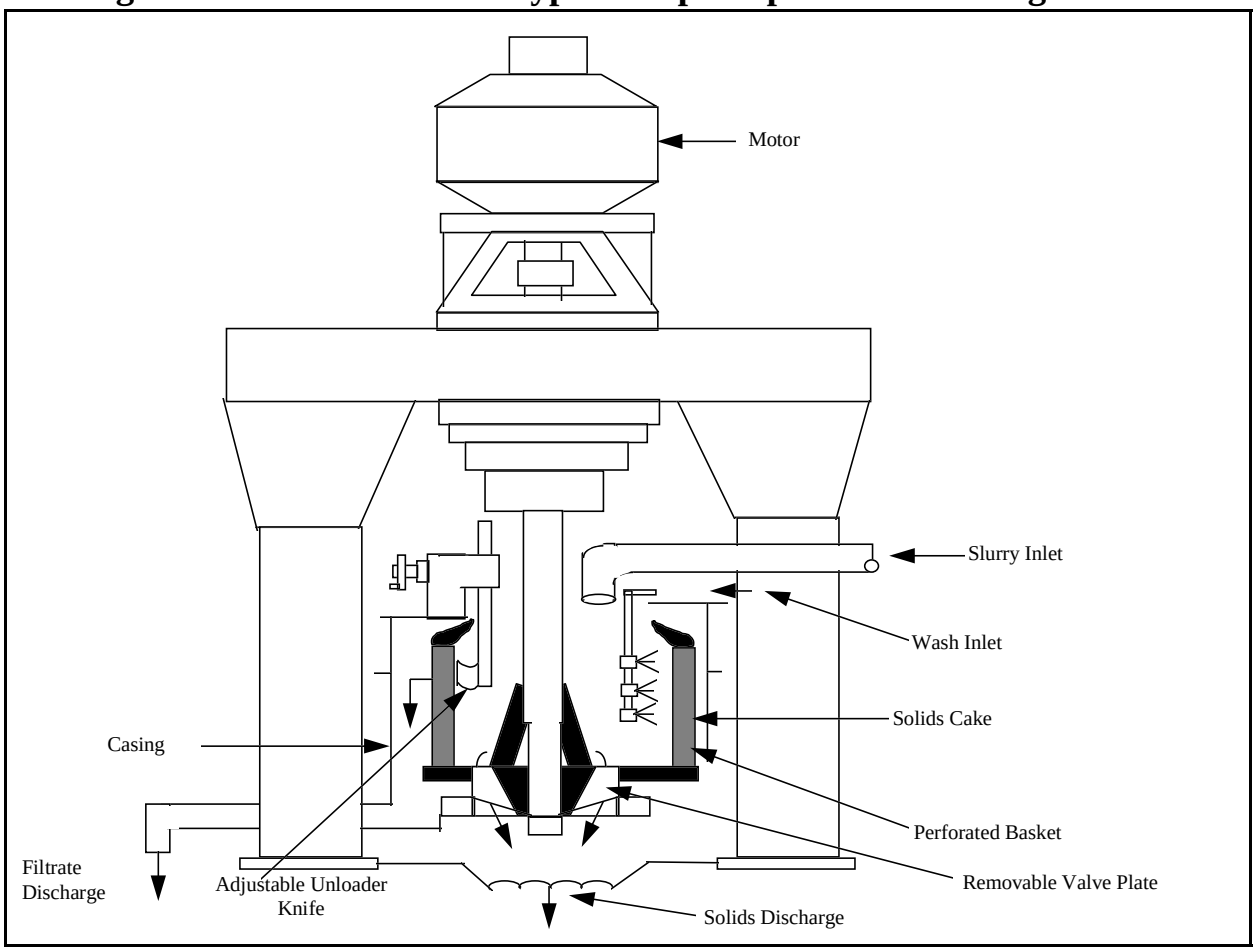
Extraction. Extraction is used to separate liquid mixtures by taking advantage of differences in the solubility of the mixture components. A solvent that preferentially combines with only one of the components is added to the mixture. "The resulting mixture consists of an extract (containing the preferentially combined material) and a raffinate (containing the residual phase). Extraction may take place in an agitated reaction vessel (mixer-settler), in a vertical cylinder (where the solvent flows upward or downward through the liquid mixture), or in a column with internals to mechanically enhance the contact between the two liquid phases" (Crume et al., 1992).

Decanting. Decanting is a simple process used to separate mixtures of a liquid and insoluble solid that has settled to the bottom of a reactor or settling vessel. The liquid over the solid is either pumped out of the vessel or poured from the vessel leaving behind the insoluble solid and a certain amount of liquid.

Centrifugation. "Centrifuges are used to remove the intermediate or product solids from a liquid stream" (USEPA 1979). Centrifuges work on the principle of centrifugal force, in which an outward force is exerted on a rotating object. Centrifuges are cylinders with rotating baskets within them. The sides of the basket are perforated and covered with filter medium such as woven fabric or metal. As the basket rotates, a slurry solution is fed into the centrifuge via an inlet pipe. The centrifugal force pushes the slurry against the rotating basket, forcing the liquid to pass through the perforations, and the solids or filter cake to remain behind, accumulating on the sides of the basket. "After all of the slurry has been fed to the chamber, a wash liquid may be introduced to force the remaining slurry liquid through the cake and

filter medium" (USEPA 1993). Once the centrifuge is turned off, the solids (i.e., the intermediates or the final bulk substance) are scraped off the sides with an internal scraper or manually scooped out. A diagram of a typical basket centrifuge is shown in Figure 7.

Figure 7: Cross-Section of Typical Top-Suspended Centrifugal Filter



Source: Adapted from *Control of Volatile Organic Compound Emissions from Batch Processes, EPA Guideline Series, 1993.*

The extremely high speeds and frictional forces involved in centrifuging, combined with the potential build-up of combustible solvent vapors, create a potential for an explosive environment to develop within the centrifuge. To control this, an inert gas, usually nitrogen, may be introduced into the unit before the slurry is fed in. "Centrifuges must be carefully operated to avoid air infiltration by vortex entrainment. Therefore, they usually are operated under nitrogen blanket and kept sealed under operation" (USEPA 1993). VOC emissions may occur when purging the vessel before loading and unloading (USEPA, 1993).

Filtration. Filtration is the separation of a fluid-solids mixture involving

passage of most of the fluid through a porous barrier (the filter medium) which retains most of the solid particulates contained in the mixture (Perry's 1984). In the pharmaceutical industry, "filtration is used to remove solids from a liquid, whether these solids be product, process intermediates, catalysts or carbon particulates (e.g., from a decoloring step)" (USEPA 1979). Batch filtration systems widely used by the pharmaceutical industry are the plate-and-frame filter, cartridge filters, the nutsche filter, and combination filter/dryers.

"The normal filtration procedure is simply to force or draw the mother liquor through a filtering medium. Following filtration, the retained solids are removed" (USEPA, 1979). The wet cake may then go through a reslurry process where it is washed and filtered again. "This option is usually carried out when a highly specialized product requiring high purity is desired or when solvents were not removed as part of the original slurry filtration (USEPA, 1993).

Crystallization

After the reaction takes place, the intermediate or final bulk substance (which is usually in solid form) can be separated from the reaction solution by crystallization. Crystallization is one of the most common separation techniques and is often used alone or in combination with one or more of the separation techniques described above. In crystallization, a supersaturated solution is created in which crystals of the desired compound are formed. Supersaturation depends on the solubility of the desired compound. If the compound's solubility increases with temperature, supersaturation can be achieved by cooling the solution. If the solubility is independent of or decreases with temperature, then evaporating a portion of the solvent will create supersaturation. "If neither cooling nor evaporation is desirable, supersaturation may be induced by adding a third component. The third component forms a mix with the original solvent in which the solute is considerably less soluble" (USEPA 1979). If crystallization is done through cooling of a solution there will be relatively little VOC emissions, especially if the equipment is fully enclosed. "However, when crystallization is done by solvent evaporation in a vacuum environment, there is a greater potential for emissions" (USEPA 1993). Further separation of the crystals from the supersaturated solution can be done by centrifuging or filtration.

Purification

Once the intermediate or the bulk substance has been separated, it may need to be purified. Depending on the intermediate or the bulk substance produced, there may be several purification steps involved to produce the desired active ingredient. In vitamin production, for example, there are at least three to four purification steps. Purification typically is achieved through additional

separation steps such as those described above. Purification is often achieved through recrystallization. Washing with additional solvents and filtration may also be used.

Drying

The final step in the chemical synthesis process is drying of the intermediate or final bulk substance. Drying is done by evaporating the solvents from the solids. Solvents released from drying operations may be condensed for reuse or disposal (USEPA 1993).

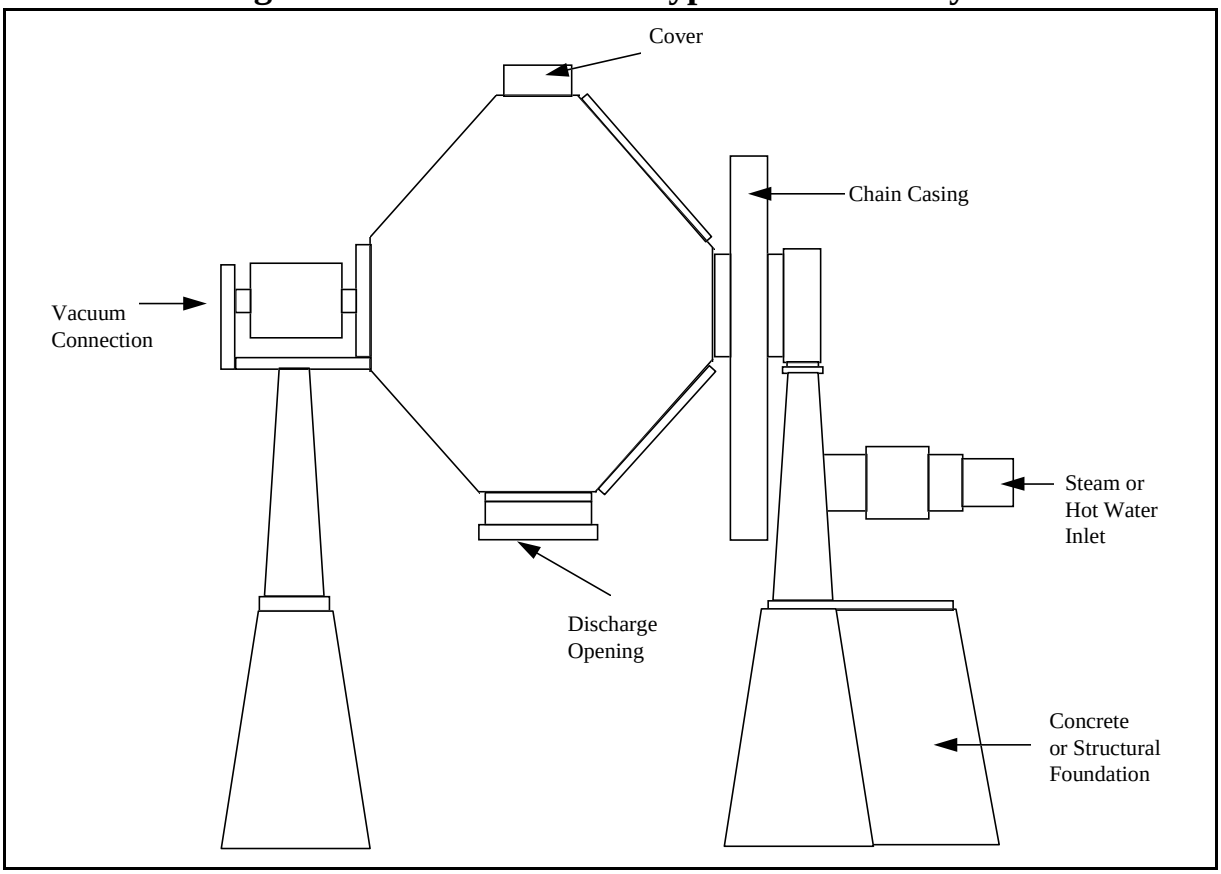
There are several different types of dryers used by the pharmaceutical industry including tray dryers, rotary dryers, drum or tumble dryers, or pressure filter dryers. "The selection of the dryer type depends primarily on the characteristics of the solid" (USEPA 1993).

Prior to 1980, probably the most common type of dryer used by the industry was the vacuum tray dryer. In a vacuum tray dryer, "the filtered solid is placed on trays which are then manually stacked on shelves in the dryer. When the dryer is closed, the trays are heated to remove any liquids. A vacuum is applied within the dryer so that drying can take place at lower temperatures when needed" (USEPA, 1993).

More often today, tumble dryers or combination filter/dryers are used. In a combination filter/dryer "the equipment not only acts as a filter, but can also function as a product dryer after the slurry has been compressed and filtered into cake form. Heat is introduced to the filter/dryer through a hot gaseous medium which is blown up through the cake until the desired level of dryness is achieved" (USEPA 1993). VOC emissions may occur since the gas will entrain evaporated solvent which must be vented from the drying filter/dryer.

Tumble dryers consist of revolving conical shells ranging in capacity from 20 to 100 gallons. "The rotation of the dryer tumbles the product to enhance solvent evaporation and may also perform a blending function" (USEPA 1979). These dryers may be operated under a vacuum or using hot air circulation. When operated under a vacuum, heat is supplied through conduction from heated surfaces. Some air will pass through the equipment due to inward leakage. Thus, the vacuum exhaust will contain VOCs (USEPA, 1993). A diagram of a simple tumble dryer is shown in Figure 8.

Figure 8: Cross-Section of Typical Tumble Dryer



Source: Adapted from *Control of Volatile Organic Compound Emissions from Batch Processes, EPA Guideline Series, 1993.*

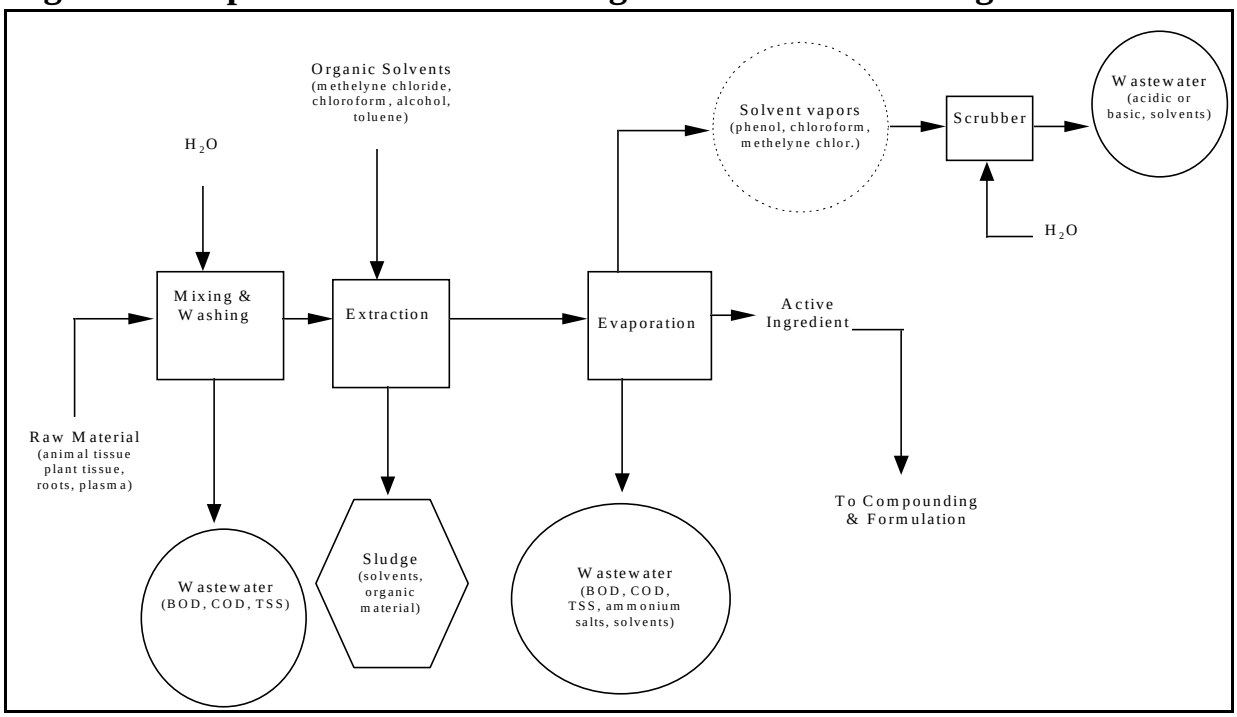
Natural and Biological Product Extraction

Natural product extraction, as the name suggests, involves isolating an active ingredient from natural sources, such as plants, roots, parasitic fungi or animal glands. This process is often used to produce allergy relief medicines, insulin, morphine, anti-cancer drugs, or other pharmaceuticals with unique properties. Blood fractionation, used to produce plasma, is also part of the natural product extraction process (USEPA 1995). A simplified diagram of natural product extraction processes and its associated wastes, is shown in Figure 9.

The desired active ingredient, usually present in raw materials at very low concentrations, must be extracted for the final product. Therefore, a defining characteristic of this process is that the volume of finished product is often an order of magnitude smaller than that of the raw materials used. At each step in the extraction process, the volume of material being processed is reduced significantly. This inherent nature of the process makes it an

expensive one to utilize (USEPA 1995).

Figure 9: Simplified Process Flow Diagram for Natural/Biological Extraction



Source: Adapted from *Economic Impact and Regulatory Flexibility Analysis of Proposed Effluent Guidelines for the Pharmaceutical Manufacturing Industry, 1995.*

Because of the large volume reductions involved, an assembly-line processing method, consisting of several operation stations is used. At each subsequent operation station, a little more of the inert material is removed and the active ingredient is extracted. As the volume of material being processed decreases, the size of the containers carrying the material also decreases, from containers capable of carrying 75-100 gallons to, in some cases, laboratory size equipment (USEPA 1995).

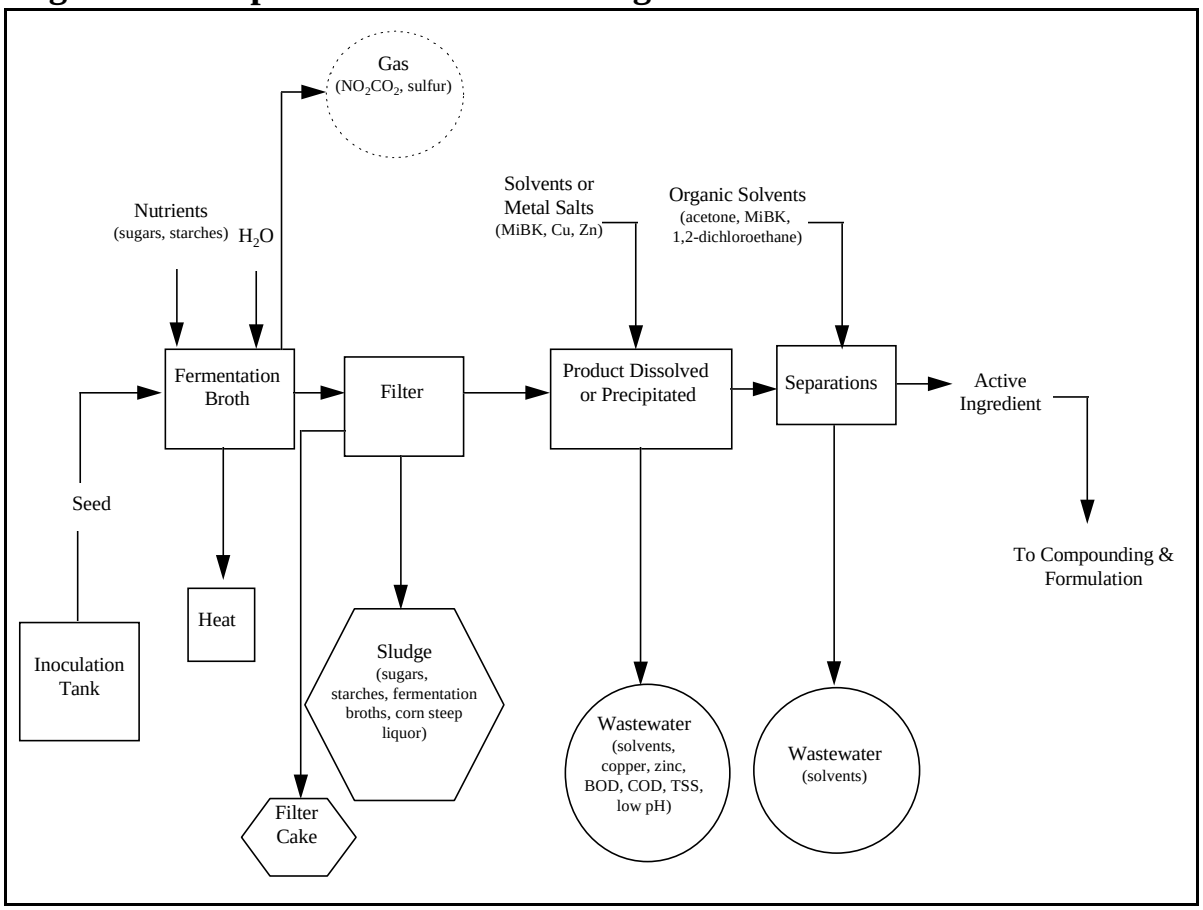
Active ingredients are recovered by precipitation, purification and solvent extraction methods. In precipitation, solubility is changed by pH adjustment, salt formation, or addition of an anti-solvent. Solvents are used as extractive agents to remove the active ingredient from the raw materials, such as plant and animal tissues. Solvents are also used to remove fats and oils, which may contaminate the product (USEPA 1995). Such solvents remove the fats and oils, without damaging the essential active ingredient(s) found in the raw materials. Ammonia is also used in the extraction stages as a method of controlling the pH when extracting from animal and plant sources. Ammonium salts are used as buffering chemicals, and aqueous or anhydrous ammonia is used as an alkalizing agent. The high degree of solubility of

ammonium salts prevents unwanted precipitation. Also, ammonium salts have the advantage of not reacting with animal and/or plant tissues (USEPA 1995).

Fermentation

Most steroids, antibiotics, and certain food additives (such as vitamins) are commonly known pharmaceuticals which are produced by fermentation. In fermentation, microorganisms (e.g., bacteria, yeast or fungi) are typically inoculated in a liquid broth supplemented with nutrients that are acclimated to an environment (e.g., temperature, pH, oxygen), conducive to rapid growth). These microorganisms produce the desired product (e.g., antibiotic, steroid, vitamin, etc.) as a by-product of normal metabolism. Fermentation involves three main steps: 1) inoculum and seed preparation, 2) fermentation, and 3) product recovery. A diagram of a fermentation process and the wastes produced in this process is shown in Figure 10.

Figure 10: Simplified Process Flow Diagram for the Fermentation Process



Source: Adapted from *Economic Impact and Regulatory Flexibility Analysis of Proposed Effluent Guidelines for the Pharmaceutical Manufacturing Industry, 1995.*

Seed Preparation

The fermentation process begins with the introduction of the microbial strain to a primary seed fermentation, which is commonly performed using shaking-flask culture techniques at the laboratory scale. Once grown, the suspension is then transferred to further seed stages, which may be additional flask fermentations, stirred tanks or both. The purpose of this "seed-train" is to generate enough inoculum for the production fermentor (typically 1-10% of the production tank volume). Generally, special seed tanks are used for the fermentor inoculum which are miniature versions (1-10% of size) of the production fermentor. If a seed tank becomes contaminated, it is emptied, sterilized, and reinoculated.

Fermentation

Once the fermentor inoculum is ready, it is charged into a sterilized fermentor. During fermentation, the fermentor is usually agitated and aerated. The pH, temperature, and dissolved oxygen content of the fermentation broth may be monitored during fermentation. Fermentation may last from hours to weeks, depending on the process. A fermentor "broth" is produced, which is then filtered or centrifuged to separate out the solids (USEPA 1991).

Product Recovery

Filtration removes any larger residues from the broth, but it does not isolate the active ingredient from the residues. This must be done by product recovery processes. Product recovery is achievable through three different methods: solvent extraction, direct precipitation and ion exchange, or adsorption (USEPA 1995). Sometimes, the active material is contained within the cells of the microorganism. Cell wall breakage by heat or ultrasound, for example, may be required to recover the material.

In solvent extraction the active ingredient is removed from the aqueous broth by contacting it with an organic solvent, in which the product is more soluble than it is in water. Removal of the active agent from the solvent can be achieved by crystallization (USEPA 1995).

The direct precipitation method of product recovery involves precipitation of the active ingredient, as a metal salt from the broth using, for example, copper (Cu) and/or zinc (Zn) as precipitating agents. The actual choice of the precipitating agent depends on the properties of the desired active ingredient. The broth is then filtered and the product is recovered from the solid residues (USEPA 1991).

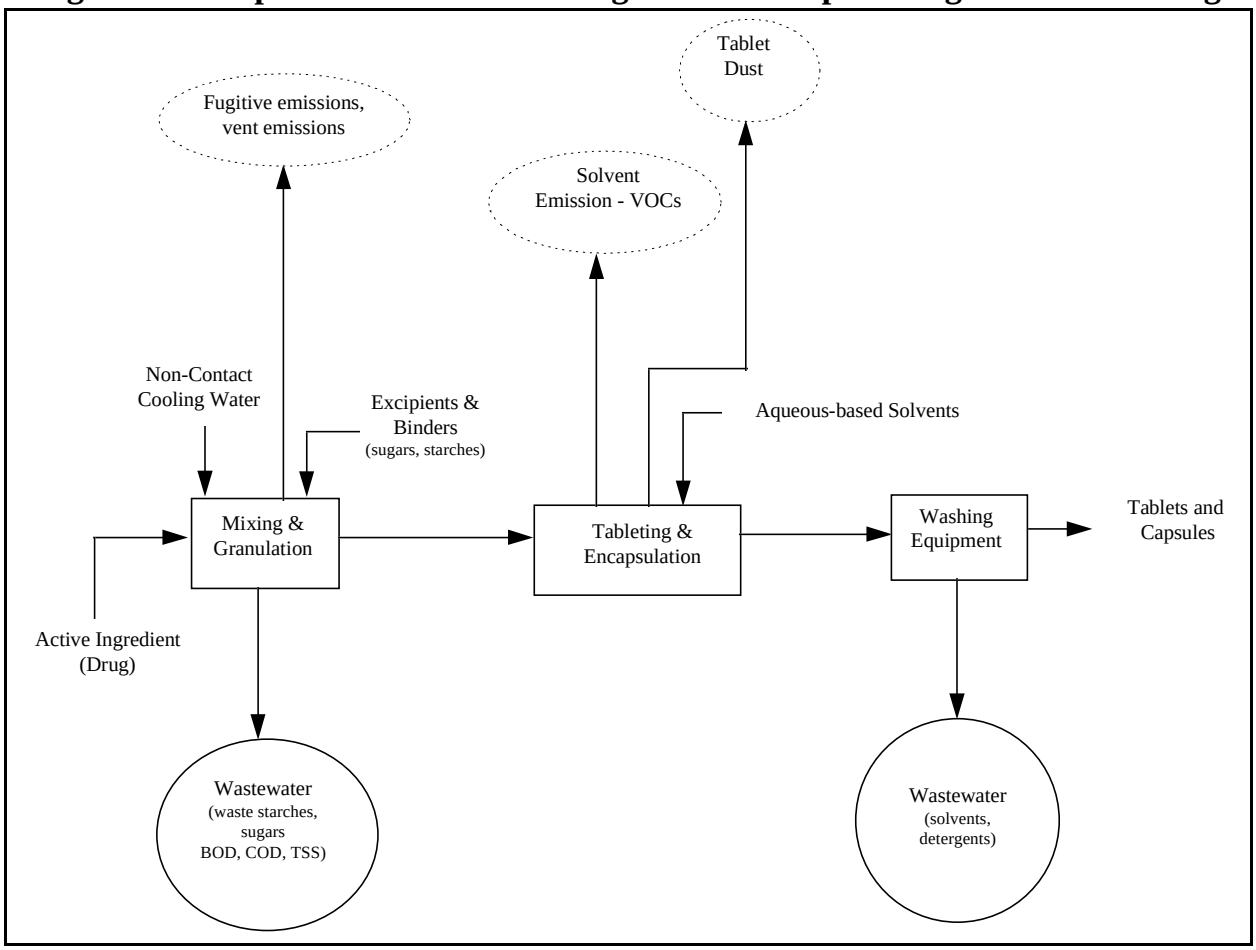
Additionally, ion exchange or adsorption may be used for product recovery.

Ion exchange resin (or alternatively, activated carbon) is contacted with the broth and the product adsorbs onto the resin. The product is recovered from the resin by using a solvent or by washing the resin with an acidic or basic solution. It is then crystallized.

III.A.3. Formulation, Mixing, and Compounding

"The primary objective of mixing, compounding, or formulating operations are to convert the manufactured bulk substances into a final, usable form." (USEPA 1995) Figure 11 shows a simplified process flow diagram for compounding, formulation and packaging. Common dosage forms of pharmaceutical products include tablets, capsules, liquids, creams and ointments, as well as aerosols, patches and injectable dosages. Table 6 lists common pharmaceutical dosage forms and their uses.

Figure 11: Simplified Process Flow Diagram for Compounding and Formulating



Source: Adapted from *Economic Impact and Regulatory Flexibility Analysis of Proposed Effluent Guidelines for the Pharmaceutical Manufacturing Industry, 1995.*

As with the bulk manufacturing operations, many final products are produced in batch utilizing a campaign regimen. At the end of the production campaign, another product may be formulated and packaged using the same equipment and the same personnel. Additionally, formulation and packaging is performed in accordance with "good manufacturing practices" (GMP). GMP is regulated by the FDA and sets forth the minimum methods to be used in, and the facilities and controls to be used for the manufacture, processing, packing, or holding of a drug to assure that such drug meets the safety requirements and the quality and purity characteristics that it purports or is represented to possess.

Following formulation, the finished product may be packaged at the same site or it may be transferred to another site. Packaging includes placing the final formulated products into containers, labeling, and preparing for shipping. "The packaging components of a pharmaceutical product are vital to its safe and effective use. Besides serving the patient as a convenient unit of use, the composite package (unit container, labeling, and shipping components) must provide appropriate identification and necessary information for proper use including warnings and (pre)cautions and preservation of the product's chemical and physical integrity" (Kirk-Othmer, 1994).

Batch production records are used and describe each manufacturing step in detail. At various stages in the formulation and packaging process, quality control checks are utilized. All raw materials are checked prior to use in a process and the final dosage forms require a myriad of tests to assure therapeutic benefit. For example, the content uniformity, color, homogeneity, dissolution, stability, identity, and potency of the product must be determined and meet stated ranges. Representative samples are collected at the end of the formulation stage and submitted to the chemical and/or microbiological laboratories for final assaying. Representative samples are also collected during packaging operations. The quality control unit of the pharmaceutical manufacturing company has the responsibility and authority to approve or reject all raw materials, in-process materials, packaging materials including containers, closures, and labeling materials, as well as the final product.

The equipment used to formulate and package the final product is cleaned, maintained, and sanitized at appropriate intervals. Actual maintenance and cleaning schedules and results are documented. As described under bulk manufacturing, the methods, equipment, and materials used (e.g., water wash, steam, detergents, organic solvents) to clean the equipment are specified on a per product basis.

Table 6: Pharmaceutical Dosage Forms

Dosage Form	Constituents, properties	Uses
	Solids	
powders, bulk	comminuted or blended, dissolved or mixed with water	external, internal
effervescent	CO_2-releasing base ingredients	oral
insufflation	insufflator propels medicated powder into body cavity	body cavities
lyophilized	reconstitution by pharmacist of unstable products	various uses including parenteral and oral
capsules	small-dose bulk powder enclosed in gelatin shell, active ingredient plus diluent	internal
troches, lozenges	prepared by piping and cutting or disk candy technology; compounded with glycerogelatin	slow dissolution in mouth
compressed tablets	dissolved or mixed with water; great variety of shapes and formulations	oral and external
pellets	for prolonged action	implantation
coated tablets	coating protective, slow release	oral
	Liquid Solutions	
syrups	sweetener, solvent, medicinal agent	flavoring agent, medicinal
spirits	alcohol, water, volatile substances	flavor or medicinal
collodions	pyroxylin in ether, medicinal agent (castor oil, camphor)	external for corns and bunions
parenteral solutions	sterile, pyrogen-free, isotonic, pH close to that of blood; oily or aqueous solution	intravenous, intramuscular, subcutaneous injection
ophthalmic	sterile, isotonic, pH close to that of tears; viscosity builder	eye treatment
nasal	aqueous, isotonic, pH close to that of nasal fluids; sprays or drops	nose treatment
mouthwash, gargles	aqueous, antiseptic	refreshment, short term bacterial control
inhalations	administered with mechanical devices	medication of trachea or bronchioles
	Liquid Dispersions	
suspensions	powder suspended in water, alcohol, glycol, or an oil	oral dosing, skin application
emulsions, lotions	oil-in-water or water-in-oil	oral, external or injection
	Semisolid and plastic dispersions	
ointments	hydrocarbon (oily), adsorptive water-washable, or water-soluble bases; emulsifying agents, glycols, medicating agent	external
pastes and cerates	ointments with high dispersed solids and waxes, respectively	external
suppositories	theobroma oil, glycinerated gelatin, or polyethylene glycol base plus medicinal agent	insertion into body cavity

Source: *Adapted from Zanowaik, P., 1995, "Pharmaceuticals"* in *Kirk-Othmer, Encyclopedia of Chemical Technology, vol. 18, 4th edition.*

Tablets

Tablets account for the majority of solid medications taken orally in the United States. "Tablets can be made to achieve rapid drug release or to produce delayed, repeated or prolonged therapeutic action" (Kirk-Othmer, 1994). Tablets can be compressed or molded, and may be coated.

To prepare a tablet, the active pharmaceutical ingredient is combined with a filler, such as sugar or starch, and a binder, such as corn syrup or starch. The filler is added to ensure that the active ingredient is diluted to the proper concentration. A binder is needed to bind tablet particles together. A lubricant, such as magnesium sterate or polyethylene glycol, may be added to facilitate equipment operation, or to slow disintegration or dissolution of the active ingredient.

Tablets are produced by compression of powder blends or granulations. In direct compression, the ingredients are blended and then compressed into the final tablet without modifying the physical nature of the material itself. "The most widely used and most general method of tablet preparation is the wet-granulation method" (Remington, 1995). In wet granulation, the active ingredient is powdered and mixed with the filler. This mixture is then wetted and blended with the binder, forming a solution. Coarse granules form which are mixed with lubricants such as magnesium stearate and then compressed into tablets. Slugging or dry granulation is used when tablet ingredients are sensitive to moisture or temperatures associated with drying or when the tablet ingredients have sufficient inherent binding or cohesive properties. Dry granulation includes weighing, mixing, slugging, dry screening, lubrication, and compression. Slugging requires large heavy presses to compress larger tablets, between 20-30 grams in weight. These large tablets are then ground and screened to a desired mesh size then recompressed into final tablets (USEPA, 1991).

Coating may be used to offer protection from moisture, oxygen, or light, to mask unpleasant taste or appearance, and to impart distinctive colors to facilitate patient recognition. "Enteric coatings are used to delay the release of the active ingredient in the stomach and prolong therapeutic activity. The latter are used for drugs that are unstable to gastric pH or enzymes, cause nausea and vomiting, or irritation to the stomach, or should be present in high concentrations in the intestines" (Kirk-Othmer, 1994). Coating is done in a rotary drum. The coating solution is poured onto the tablets. In many operations, aqueous coating solutions are now used instead of solvent based (usually methylene chloride) solutions. As the drum rotates, the tablets become coated. Once coated, they are dried in the drum and may be sent to another rotary drum for polishing. Polishing works by the friction created

when the tablets rotate and rub against each other. Un-coated tablets may also be polished.

Once the tablets pass quality control requirements, they may be held or sent directly to packaging. Coated tablets are stamped with identifying information (e.g., brand name, code number) in a rotary ink press.

Capsules

After tablets, the most common solid oral dosage form is the capsule. Capsules come in soft and hard shelled varieties. Hard capsules or "dry-filled" capsules are formed by dipping metal pins into a solution of gelatin of a specific temperature. The temperature controls the viscosity of the gelatin and hence the thickness of the capsule walls. When the pins are removed from the solution, a hard coating of gelatin forms on the pins. The coating is dried and trimmed. "These capsules are filled by introducing the powdered material into the longer end or body and the capsule and then slipping on the cap." (Remington, 1995)

Soft shelled capsules are formed by placing two continuous gelatin films between rotary die plates. As the plates are brought together, the two gelatin films join and seal, forming the two halves of the capsule. As the two halves join, the ingredients, which can be a liquid, paste or powder, are injected into the capsules. "Commercially filled soft gelatin capsules come in a wide choice of sizes and shapes: they may be round, oval, oblong, tube or suppository-shaped" (Remington).

Liquid Dosage

In formulating a liquid product, the ingredients are first weighed and then dissolved in an appropriate liquid. The solutions are mixed in glass-lined or stainless steel vessels, after which they are stored in tanks before final packaging. Preservatives may be added to prevent mold and bacterial growth. If the liquid will be used for injection or ophthalmic use, sterilization is required. In this case, the container, which has also been previously sterilized/depyrogenated, is filled with liquid which has either been rendered sterile by aseptic filtration in a sterile environment and/or the entire container and its contents are terminally heat sterilized in an autoclave.

Ointments and Creams

Ointments are usually made by blending the bulk active ingredient with a base, such as a petroleum derivative or wax. The mixture is cooled, rolled out, and poured into tubes by machines and packaged (USEPA, 1991).

Creams are semisolid emulsions and are either oil-in-water or water-in-oil, rather than being petroleum based. "Generally, the ingredients of the two phases are heated separately, then are mixed and stirred vigorously to achieve emulsification" (Kirk-Othmer, 1994).

As with all other dosage forms, equipment is washed and cleaned based on batch record requirements. However, because of the greasy nature of ointment and cream production, cleaning often is done with detergents.

III.B. Raw Material Inputs and Pollutant Outputs

Pharmaceutical batch processes use numerous raw materials and generate wastes and emissions. In general, the waste and emissions generated depend on the raw materials and equipment used, as well as the manufacturing process employed. In designing bulk manufacturing processes, consideration is given to the availability of the starting materials and their toxicity, as well as the wastes (e.g., mother liquors, filter residues, and other by-products) and the emissions generated. A description of some of the considerations given is provided in Section V, Pollution Prevention Opportunities.

When bulk manufacturing reactions are complete, the solvents are physically separated from the resulting product. Due to purity concerns, solvents often are not reused in a pharmaceutical process. They may be sold for non-pharmaceutical uses, used for fuel blending operations, recycled, or destroyed through incineration.

This section describes the raw materials and associated waste streams and some of the more common technologies used to control these wastes. Much of this information is summarized in Table 7.

Table 7: Summary of Typical Material Inputs and Pollution Outputs in the Pharmaceutical Industry

Process	Inputs (examples of some commonly used chemicals provided)	Air Emissions	Wastewater	Residual Wastes
Chemical Synthesis - *Reaction*	Solvents, catalysts, reactants, e.g. benzene, chloroform, methylene chloride, toluene, methanol, ethylene glycol, methyl isobutyl ketone (MiBK), xylenes, hydrochloric acid, etc.	VOC emissions from reactor vents, manways, material loading and unloading, acid gases (halogen acids, sulfur dioxide, nitrous oxides); fugitive emissions, from pumps, sample collections, valves, tanks	Process waste waters with spent solvents, catalysts, reactants; pump seal waters, wet scrubber wastewater; equipment cleaning wastewater; wastewater maybe high in BOD, COD, TSS with pH of 1-11.	Reaction residues and reactor bottom wastes
- *Separation*	Separation and extraction solvents, e.g.. methanol, toluene, hexanes, etc.	VOC emissions from filtering systems which aren't contained; and fugitive emissions from valves, tanks and centrifuges	Equipment cleaning wash waters, spills, leaks, spent separation solvents	
- *Purification*	Purification solvents e.g.. methanol, toluene, acetone, hexanes, etc.	Solvent vapors from purification tanks; fugitive emissions	Equipment cleaning wash waters, spills, leaks, spent purification solvents	
- *Drying*	Finished active drug(s) or intermediates	VOC emissions from manual loading and unloading of dryers	Equipment cleaning wash waters, spills, leaks	
Natural Product Extraction	Plants, roots, animal tissues, extraction solvents, e.g.. ammonia, chloroform, phenol, toluene, etc.	Solvent vapors & VOC's from extraction chemicals	Equipment cleaning wash waters, spent solvents (ammonia); natural product extraction wastewater have low BOD, COD, TSS and pH of 6-8.	Spent raw materials (plants, roots etc.)
Fermentation	Inoculum, sugars, starches, nutrients, phosphates, fermentation solvents, e.g.. ethanol, amyl alcohol, methanol, MiBK, acetone, etc.	Odoriferous gases, extraction solvent vapors, particulates	Spent fermentor broth, fermentation wastewater containing sugars, starches, nutrients, etc.; wastewater tends to have high BOD, COD, TSS and have pH of 4-8.	Waste filter cake, fermentation residues
Formulation	Active drug, binders (starches), sugar, syrups, etc.	Tablet dusts, other particulates	Equipment cleaning wash waters (spent solvents), spills, leaks; wash waters typically contain low levels of BOD, COD, TSS and have pH of 6-8.	Particulates, waste packaging, rejected tablets, capsules etc.

Source: Development Document for Proposed Effluent Limitations Guidelines and Standards for the Pharmaceutical Manufacturing Point Source Category, US EPA, Washington, DC., February 1995.

III.B.1. Raw Materials

"The pharmaceutical manufacturing industry draws upon worldwide sources for the myriad of raw materials it needs to produce medicinal chemicals. Fermentation operations require many new raw materials falling into general chemical classifications such as carbohydrates, carbonates, steep liquors, nitrogen, and phosphorus compounds, anti-foam agents, and various acids and bases. These chemicals are used as carbon and nutrient sources, as foam control additives, and for pH adjustment in fermentation processes. Various solvents, acids, and bases are also required for extraction and purification processes.

Hundreds of raw materials are required for the chemical synthesis processes used by the industry. These include organic and inorganic compounds and are used in gas, liquid, and solid forms. Plant and animal tissues are also used by the pharmaceutical manufacturing industry to produce various biological and natural extraction products" (EPA, 1995).

Each manufacturing or formulation plant is special, differing from other similar pharmaceutical plants in size, types of intermediates, bulk substances, or products produced, amounts and types of solvents used, and thus, in the raw materials used and wastes/emissions generated. Most bulk pharmaceutical reactions require organic solvents to dissolve chemical intermediates and reagents. Because of the high reactivity of many pharmaceutical reagents and intermediates, pharmaceutical solvents must be non-reactive, provide an environment which allows efficient heat transfer during endothermic or exothermic reactions, and facilitate efficient electron transfer. Often halogenated solvents, such as methylene chloride, provide the optimum choice for pharmaceutical reactions. The most commonly used solvent in the pharmaceutical industry is methanol, an oxygenated organic solvent. Other common solvents used are ethanol, acetone, and isopropanol. Tables 8, 9, and 10 show the typical solvents (and whether or not they are priority pollutants or hazardous air pollutants) used in chemical synthesis, biological and natural extraction, and fermentation processes, respectively.

Final bulk substances from the bulk manufacturing processes are used in formulation operations, along with other raw materials or ingredients. The production of these ingredients is described under Section III.A.2.

Table 8: Solvents Used in the Chemical Synthesis Process

Chemical	Priority Pollutant Under the Clean Water Act	Hazardous Air Pollutant under the Clean Air Act	Chemical	Priority Pollutant Under the Clean Water Act	Hazardous Air Pollutant under the Clean Air Act
Acetone			Ethylene glycol		X
Acetonitrile		X	Formaldehyde		X
Ammonia (aqueous)			Formamide		
n-Amyl acetate			Furfural		
Amyl Alcohol			n-Heptane		
Aniline		X	n-Hexane		X
Benzene	X	X	Isobutyraldehyde		
2-Butanone (MEK)		X	Isopropanol		
n-Butyl acetate			Isopropyl acetate		
n-Butyl alcohol			Isopropyl ether		
Chlorobenzene	X	X	Methanol		X
Chloroform	X	X	Methylamine		
Chloromethane	X	X	Methyl cellulose		
Cyanide	X		Methylene chloride	X	X
Cyclohexane			Methyl formate		
o-Dichlorobenzene (1,2-Dichlorobenzene)	X		Methyl isobutyl ketone (MiBK)		X
1,2-Dichlorobenzene	X		2-Methylpyridine		
Diethylamie			Petroleum naphtha		
Diethyl Ether			Phenol	X	X
N,N-Dimethyl acetamide			Polyethylene glycol 600		
Diethylamine			n-Propanol		
N,N-Dimethylaniline		X	Pyridine		
N,N-Dimethylformamide		X	Tetrahydrofuran		
Dimethyl sulfoxide			Toluene	X	X
1,4-Dioxane		X	Trichlorofloromethane		
Ethanol			Triethylamine		X
Ethyl acetate			Xylenes		X

Source: *adapted from Development Document for Proposed Effluent Guidelines and Standards for the Pharmaceutical Manufacturing Point Source Category, 1995 and US Environment Laws, 1994.*

Table 9: Solvents Used in Biological and Natural Product Extraction					
Chemicals	**Priority Pollutants under the Clean Water Act**	**Hazardous Air Pollutants under the Clean Air Act**	**Chemicals**	**Priority Pollutants under the Clean Water Act**	**Hazardous Air Pollutants under the Clean Air Act**
Acetone			Ethylene glycol		X
Acetonitrile		X	Formaldehyde		X
Ammonia (aqueous)			n-Heptane		
n-Amyl acetate			n-Hexane		X
Amyl alcohol			Isopropanol		
n-Butyl alcohol			Isopropyl acetate		
Chloroform	X	X	Isopropyl ether		
1,2-Dichloroethane	X		Methanol		X
Diethylamine			Methylene chloride	X	X
Diethyl ether			Petroleum naphtha		
N,N-Diethylformamide		X	Phenol	X	X
Dimethyl sulfoxide			n-Propanol		
1,4-Dioxane		X	Pyridine		
Ethanol			Tetrahydrofuran		
Ethyl acetate			Toluene	X	X

Source: *adapted from Development Document for Proposed Effluent Guidelines and Standards for the Pharmaceutical Manufacturing Point Source Category, 1995 and US Environment Laws, 1994.*

Table 10: Solvents Used in Fermentation Processes					
Chemicals	**Priority Pollutants Under the Clean Water Act**	**Hazardous Air Pollutants under the Clean Air Act**	**Chemicals**	**Priority Pollutants Under the Clean Water Act**	**Hazardous Air Pollutants under the Clean Air Act**
Acetone			n-Heptane		
Acetonitrile		X	n-Hexane		X
Ammonia (aqueous)			Isopropanol		
n-Amyl acetate			Isopropyl acetate		
Amyl alcohol			Methanol		X
n-Butyl acetate			Methyl cellulose		
n-Butyl alcohol			Methylene chloride	X	X
Chloroform	X	X	Methyl isobutane ketone (MiBK)		X
N,N-Diethylformamide		X	Petroleum naphtha		
Ethanol			Phenol	X	X

Table 10: Solvents Used in Fermentation Processes					
Ethyl acetate			Toluene	X	X
Formaldehyde		X	Triethylamine		X

Source: *adapted from Development Document for Proposed Effluent Guidelines and Standards for the Pharmaceutical Manufacturing Point Source Category, 1995 and US Environment Laws, 1994.*

III.B.2. Air Emissions and Control Systems

Both gaseous organic and inorganic compounds, as well as particulates, may be emitted during pharmaceutical manufacturing and formulation. Some of the volatile organic compounds (VOC) and inorganic gases that are emitted are classified as hazardous air pollutants (HAPs) under the Clean Air Act.

The type and amount of emissions generated are dependent on the operations conducted by the facility, as well as how the product is manufactured or formulated. "Each (pharmaceutical) plant is unique, differing from other plants in size, types of products manufactured, amounts and types of VOC used, and air pollution control problems encountered" (EPA, 1979).

Bulk Manufacturing

As previously described, the industry manufactures most bulk pharmaceutical substances and intermediates in campaigns via batch processes. Following the completion of one campaign, another bulk substance or intermediate is typically made using the same equipment (e.g., reactors, filters, dryers). The reactants and solvents used in manufacturing the next bulk substance or intermediate may vary greatly from the ones previously used. While some reactions may require the use of halogenated solvents, the next reaction may use another solvent or no solvent at all.

This wide variations in bulk manufacturing makes predicting typical or annual average emissions difficult. This is because the emission generated are predicated on what bulk substance or intermediate is manufactured and over what length of time, and which equipment and raw materials are used. Some bulk substances and intermediates are made frequently, while others may be made only once every two to three years over a one to two week period. This has often prevented the calculation of typical emission rates for each operation. However, an approximate ranking of emission sources has been established by EPA and is presented below in order of decreasing magnitude. The first four sources generally will account for the majority of emissions from a bulk manufacturing plant.

- Dryers
- Reactors
- Distillation units
- Storage and transfer of materials

- Filtration
- Extraction
- Centrifugation
- Crystallization

Dryers are one of the largest sources of VOC emissions in bulk manufacturing. In addition to the loss of solvent during drying, manual loading and unloading of dryers can release solvent vapors into ambient air, especially when tray dryers are used. VOCs are also generated from reaction and separation steps via reactor vents and manways. Centrifuges may be a source of VOC emissions, especially in top loading types, where solids are manually scooped out.

Typical controls for these emission sources, excluding storage and transfer operations, include condensers, scrubbers, carbon absorbers and, on occasion, incinerators. "Storage and transfer emissions can be controlled by vapor return lines, vent condensers, conservation vents, vent scrubbers, pressure tanks and carbon absorbers. Floating roofs may be feasible controls for large vertical storage tanks" (EPA, 1979).

Formulation

Both particulates and VOCs may be formed during mixing, compounding, formulation, and packaging steps. Because these compounds may pose a danger to workers, through direct inhalation, they are a principal concern. Depending on the process and the batch record requirements, the particulates (e.g., tablet dusts) may be recycled back into the formulation process. However, sometimes the particulates are collected for destruction or disposal.

As in bulk manufacturing, the type and quantity of compounds emitted depends on the operation. For example, formulation facilities may or may not emit VOCs. Some formulation operations do not require the use of solvents, some may only use solvents for cleaning, and some may use solvents in granulation and coating operations. In some facilities, organic compounds, such as ethanol or isopropyl alcohol, might be used in the formulation of the product and VOCs may be emitted during mixing, formulation, and/or packaging.

Air Pollution Control Equipment

More than one type of air control equipment may be used at any one time in any one facility. A description of the various equipment used by the industry is provided below.

Condensers. Condensers are widely used in the pharmaceutical industry to recover solvents from process operations (a process condenser) and as air pollution control devices to remove VOCs from vented gases. Process condensers differ from condensers used as air pollution control devices as the primary purpose of a process condenser is to recover material as an integral part of a unit operation. The process condenser is the first condenser located after the process equipment and supports a vapor-to-liquid phase change for the vapors produced in the process equipment. Examples of process condensers include distillation condensers, reflux condensers, process condensers in line before the vacuum source, and process condensers used in stripping or flashing operations. The primary purpose of a condenser used as an air pollution control device is to remove VOCs prior to venting.

Condensation is the process of converting a gas or vapor to liquid. In this method, gas streams from vents containing VOCs are cooled to below their saturation temperatures, converting the gas into a VOC liquid. This removes some VOCs from the gas, but some remains. The amount of VOCs remaining in the gas depends on the temperature and vapor-liquid equilibrium of the VOC. Lowering the temperature of the condenser generally lowers the content of VOC in the gas stream.

"In the most common type, surface condensers, the coolant does not directly contact condensable vapors, rather heat is transferred across a surface (usually a tube wall) separating vapor and coolant. In this way the coolant is not contaminated with condensed VOC and may be directly reused. The type of coolant used depends on the degree of cooling needed for a particular situation" (EPA, 1979). Coolants in common use are water, chilled water, brine, and glycol.

Scrubbers. Scrubbers or gas absorbers are used to remove one or more constituents from a gas stream by treatment with a liquid. "Absorption is important in the pharmaceutical industry because many VOCs and other chemicals being used are soluble in water or aqueous solutions. Therefore, water, caustic or acidic scrubbers can be applied to a variety of air pollution problems" (USEPA 1979).

When using a scrubber as an air pollution control device, the solubility of the constituents in the gas stream in the absorbing liquid must be determined. "The rate of transfer of the soluble constituents from the gas to the liquid phase is determined by diffusional processes occurring on each side of the gas liquid interface" (Theodore and Bonicore, 1989).

The main types of scrubbers used are packed tower, plate or tray tower, venturi scrubber, and spray tower. Each type of scrubber is designed to provide intimate contact between the scrubbing liquid and the gaseous

constituents so that mass transfer between phases is promoted. The degree of control achieved is dependent on the residence time of the gas and liquids, the interfacial area, and the physical and thermodynamic properties of the VOC species involved.

Combustion or Incineration. Another method used for controlling VOC emissions is combustion or incineration. "In general, factors that influence the efficiency of combustion are: (1) temperature, (2) degree of mixing, (3) residence time in the combustion chamber, and (4) type of VOC combusted. Since more waste streams contain dilute VOC concentrations, they require that supplemental fuel maintain the necessary combustion temperatures" (EPA, 1979). Although combustion systems can achieve high removal efficiencies, these systems are typically more expensive to install, operate, and maintain, and have secondary emissions associated with their operation. Additionally, a scrubber may be required to control inorganic gases produced as by-products of combustion.

"Equipment used to control waste gases by combustion can be divided into three categories: direct combustion or flaring (not often used by the pharmaceutical industry), thermal oxidation, and catalytic oxidation. A direct combustor or flare is a device in which air and all the combustible waste gases react at the burner. In contrast, in thermal oxidation, the combustible waste gases pass over or around a burner flame into a residence chamber where oxidation of the waste gases is completed. Catalytic oxidation is very similar to thermal oxidation. The main difference is that after passing through the flame area, the gases pass over a catalyst bed which promotes oxidation at a lower temperature than does thermal oxidation" (Theodore and Buonicore, 1989). Efficiency rates of catalytic oxidizers in destroying VOCs can reach close to 98% (Buonicore and Davis, 1992).

Adsorption. Adsorption is another method for removing VOCs from gas streams. This method filters out the volatiles by passing them through a packed column of activated carbon, silicates, aluminas, aluminosilicates, or any other surface which is porous and has a microcrystalline structure. As the gas stream passes through the column, the VOCs adsorb to the surface of the media. The adsorption material in the column eventually becomes saturated, and must be either regenerated or disposed. Most sorbents may be regenerated repeatedly by passing hot gas or steam through the bed. VOCs will desorb into the gas or steam. The high VOC concentration in the gas or steam can then be removed through condensation. Adsorption can be about 98% efficient in removing VOCs in the waste gas stream (Crume and Portzer, 1992).

III.B.3. Wastewater

Pharmaceutical manufacturers use water for process operations, as well as for other non-process purposes. However, the use and discharge practices and the characteristics of the wastewater will vary depending on the operations conducted at the facility. Additionally, in some cases, water may be formed as part of a chemical reaction.

Process water includes any water that, during manufacturing or processing, comes into direct contact with or results from the use of any raw material or production of an intermediate, finished product, byproduct, or waste. Process wastewater includes water that was used or formed during the reaction, water used to clean process equipment and floors, and pump seal water. Non-process wastewater includes noncontact cooling water (e.g., used in heat exchangers), noncontact ancillary water (e.g., boiler blowdown, bottle washing), sanitary wastewater, and wastewater from other sources (e.g., storm water runoff).

Based on the responses from 244 facilities to a 1990 308 Questionnaire, EPA estimated the average daily wastewater generation by the pharmaceutical manufacturing industry to be 266 million gallons. Additionally, EPA learned that more than half of the responding facilities have implemented water conservation measures. Such measures include: careful monitoring of water use, installation of automatic monitoring and alarm systems or in-plant discharges, implementation of alternative production processes, reuse of non-contact water as process makeup water and treatment of contact cooling water to allow reuse.

Pharmaceutical manufacturers generate process wastewater containing a variety of conventional parameters (e.g., BOD, TSS, and pH) and other chemical constituents. The top ten chemicals discharged by the pharmaceutical industry are provided in Table 11. Of these compounds, two are "priority pollutants"[3]. The top four compounds are oxygenated organic solvents (e.g., methanol, ethanol, acetone, and isopropanol).

[3] Priority pollutants are the pollutants listed in 40 CFR part 403, Appendix A.

Table 11: Chemicals Discharged in Wastewater by the Pharmaceutical Manufacturing Industry

Constituent Name	Quantity Discharged (lbs/yr)	Percent of Total Loading	# of Facilities Reporting Constituents
Methanol	15,388,273	28	82
Ethanol	6,802,384	12	97
Acetone	4,573,766	8.4	55
Isopropanol	4,565,370	8.4	85
Acetic acid	4,328,691	7.9	44
Methylene chloride	3,590,640	6.6	47
Formic acid	2,136,059	3.9	9
Ammonium hydroxide	1,365,741	2.5	32
N_1N-Dimethylacetamide	1,046,333	1.9	7
Toluene	783,364	1.4	43

Source: *adapted from Development Document for Proposed Effluent Guidelines and Standards for the Pharmaceutical Manufacturing Point Source Category, 1995 and US Environment Laws, 1994.*

Most process wastewater receives some treatment, either in-plant at the process unit prior to commingling with other facility wastewater or prior to discharge to a permitted outfall. Table 12 provides a trend analysis prepared by EPA of wastewater treatment technologies used by the pharmaceutical industry. EPA found that "since 1986, the use of neutralization, equalization, activated sludge, primary clarification, multimedia filtration, steam stripping, secondary clarification, granular activated carbon, and oxidation have all increased, while the use of aerated lagoons, chlorination, waste stabilization ponds, and trickling filters have decreased slightly" (USEPA 1995).

More than half of the surveyed facilities provide pH adjustment or neutralization to adjust the pH prior to discharge. Additionally, because wastewater treatment can be sensitive to spikes of high flow or high constituent concentration, many treatment systems include equalization. Advanced biological treatment is used to treat biochemical oxygen demand (BOD_5), chemical oxygen demand (COD), total suspended solids (TSS), as well as various organic constituents. Biological systems can be divided into two basic types: aerobic (treatment takes place in the presence of oxygen) and anaerobic (treatment takes places in the absence of oxygen). Very few pharmaceutical facilities (only two) use anaerobic treatment. However, more than 30 percent use aerobic systems such as activated sludge, aerated lagoons, trickling filter, and rotating biological contactors (RBC).

Table 12: Wastewater Treatment Technology Trends		
Treatment Technology	**Percentage of Facilities Using Technology Prior to 1986**	**Percentage of Facilities Using Technology in 1989/1990**
Neutralization	26.0	44.3
Equalization	20.1	28.6
Activated sludge	16.9	20.5
Settleable solids removal	13.3	NA
Primary sedimentation	12.0	NA
Aerated lagoon	7.5	4.9
Primary clarification	3.9	9.8
Chlorination	3.6	2.5
Polishing ponds	3.2	NA
Waste stabilization pond	2.9	2.5
Trickling filter	2.9	2.0
Multimedia filtration	2.3	6.1
Stream stripping	1.9	5.7
Evaporation	1.9	NA
Secondary clarification	1.6	20.9
Granular activated carbon	1.3	3.3
Oxidation	1.0	2.0
Dissolved air flotation	1.0	NA
pH adjustment	NA	50.0
Phase separation	NA	12.3

Note: Total percentage is not 100 because facilities may use multiple treatment technologies.
NA - Not available.

Source: *adapted from Development Document for Proposed Effluent Guidelines and Standards for the Pharmaceutical Manufacturing Point Source Category, 1995 and US Environment Laws, 1994.*

Although the pharmaceutical industry has routinely utilized recovery systems to recover and reuse solvents, only four facilities were identified by EPA as using stream stripping to remove gases and/or organic chemicals from wastewater streams. Sixty one facilities were identified that use distillation either to recover a specific solvent from a process stream or to treat one or more process waste streams. However, according to PhRMA, it is likely that these facilities use this method to recover a specific solvent from a specific

process stream rather than to treat wastewater from numerous operations since the treatment technology is not applicable to the wide range of waste characteristics common in the pharmaceutical industry.

III.B.4. Solid Wastes

Both nonhazardous and hazardous wastes are generated during all three stages of pharmaceutical manufacturing. These wastes can include off-spec or obsolete raw materials or products, spent solvents, reaction residues, used filter media, still bottoms, used chemical reagents, dusts from filtration or air pollution control equipment, raw material packaging wastes, laboratory wastes, spills, as well as wastes generated during packaging of the formulated product.

Filter cakes and spent raw materials (plants, roots, animal tissues etc.) from fermentation and natural product extraction are two of the largest sources of residual wastes in the pharmaceutical industry. Other wastes include reaction residues and filtrates from chemical synthesis processes. These wastes may be stripped of any solvents which remain in them, and then disposed as either hazardous or nonhazardous wastes. Typically, solid wastes are shipped off-site for disposal or incineration.

A number of practices are implemented by the industry to reduce waste generation and material losses. Typical practices include process optimization, production scheduling, materials tracking and inventory control, special material handling and storage procedures, preventive maintenance programs, and waste stream segregation.

III.C. Management of TRI Chemicals in the Production Process

The Pollution Prevention Act of 1990 (PPA) requires facilities to report information about the management of Toxics Release Inventory (TRI) chemicals in waste and efforts made to eliminate or reduce those quantities. These data have been collected annually in Section 8 of the TRI reporting Form R beginning with the 1991 reporting year. The data summarized below cover the years 1994 through 1997 and are meant to provide a basic understanding of the quantities of waste handled by the industry, the methods typically used to manage this waste, and recent trends in these methods. TRI waste management data can be used to assess trends in source reduction within individual industries and facilities, and for specific TRI chemicals. This information could then be used as a tool in identifying opportunities for pollution prevention compliance assistance activities.

While the quantities reported for 1994 and 1995 are estimates of quantities already managed, the quantities reported for 1996 and 1997 are projections only. The PPA requires these projections to encourage facilities to consider future waste generation and source reduction of those quantities as well as movement up the waste management hierarchy. Future-year estimates are not commitments that facilities reporting under TRI are required to meet.

Table 13 shows that the TRI reporting pharmaceutical facilities managed about 382 million pounds of production related wastes (total quantity of TRI chemicals in the waste from routine production operations in Column B) in 1995. From the yearly data presented in Column B, the total quantity of production related wastes increased between 1994 and 1995. This is probably in part because the number of chemicals on the TRI list almost doubled between those years. The quantity of wastes generated was also projected to increase in 1996 and 1997. The effect of production increases on the amount of wastes generated has not been evaluated.

Values in Column C are intended to reveal the percentage of TRI chemicals that are either transferred off-site or released to the environment. Column C is calculated by dividing the total TRI transfers and releases (reported in Sections 5 and 6 of the TRI Form R) by the total quantity of production-related waste (reported in Section 8 of Form R). Column C shows a decrease in the portion either transferred off-site or released to the environment from 50 percent in 1994 to 46 percent in 1995. The waste released to the environment or transferred off-site for disposal decreased slightly in 1995 to about 10 percent of total wastes generated, as shown in Column J. This decreasing trend is projected to continue through 1997.

The overall proportions of wastes managed off-site (Columns D, E, and F) and onsite (Columns G, H, and I) change very little from year to year. About 50 percent of the industry's TRI wastes were managed on-site through recycling, energy recovery, or treatment as shown in columns D, E, and F, respectively. Almost all of these on-site managed wastes were recycled or treated on-site. Only about two percent were used in energy recovery. Waste that is transferred off-site can be divided into portions that are recycled off-site, recovered for energy off-site, or treated off-site as shown in columns G, H, and I, respectively. The remaining portion of the production related wastes, 10 percent, shown in column J, is either released to the environment through direct discharges to air, land, water, and underground injection, or it is disposed off-site.

Table 13: Source Reduction and Recycling Activity for the Pharmaceuticals Industry as Reported within TRI

A	B	C	On-Site			Off-Site			J
			D	E	F	G	H	I	
Year	Quantity of Production-Related Waste (10^6 lbs.)[a]	% Released and Transferred[b]	% Recycled	% Energy Recovery	% Treated	% Recycled	% Energy Recovery	% Treated	% Released and Disposed[c] Off-site
1994	324	50%	13.9%	2.0%	33.5%	5.3%	21.7%	13.3%	10.8%
1995	382	46%	16.8%	1.6%	34.3%	4.7%	21.6%	11.7%	9.7%
1996	404	NA	18.7%	1.6%	37.1%	5.1%	18.8%	10.4%	8.4%
1997	414	NA	20.4%	1.6%	35.9%	5.5%	18.4%	9.9%	8.3%

Source: *Toxics Release Inventory Database, 1995.*

[a] Within this industry sector, non-production related waste < 1% of production related wastes for 1995.

[b] Total TRI transfers and releases as reported in Section 5 and 6 of Form R as a percentage of production related wastes.

[c] Percentage of production related waste released to the environment and transferred off-site for disposal.